

# Returns on research funded under the NIHR Health Technology Assessment (HTA) Programme

Economic analysis and case studies

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# Preface

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The Department of Health (England) requested that RAND Europe conduct an economic analysis of the impact of the HTA Programme. This report describes the results of that work, which consisted of analysis of the potential economic benefits of a sample of HTA funded studies and comparison to programme costs, supplemented by a set of short case studies exploring the impacts of the HTA Programme on policy and practice. This is an independent report commissioned and funded by the Policy Research Programme in the Department of Health. The views expressed are not necessarily those of the department.

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## Summary

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The NIHR's Health Technology Assessment (HTA) Programme was established in 1993 and is the largest dedicated research programme for the National Health Service (NHS). The Health Technology Assessment (HTA) programme funds 'independent research about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS.'<sup>3</sup> The purpose of the programme is to ensure that high quality research evidence is made available on the effectiveness, costs and impact of health technologies to policymakers, practitioners and patients in a timely and efficient manner. The work of the HTA Programme covers both primary research and evidence synthesis. The research is either commissioned or researcher-led. The underlying principle of the HTA Programme is that clinical research should not only use the most rigorous techniques, but should be needs-led, with a clear benefit to patients and practitioners.

The Department of Health (DH) wants to know the benefits that would have been available to the health system, and the wider community, if the findings of HTA studies had been implemented. Because the implementation of these findings is outside of the scope of the HTA programme, considering the extent of adoption is not included in the economic analysis conducted here. Instead, we focus on measuring what the potential benefits of adoption could be. HTA-funded research can deliver economic benefits in a range of ways. In the economic analysis conducted here, we focus on the benefits of showing a new intervention should be implemented. In this context, benefit can be delivered in two ways:

- By demonstrating a new intervention improves health outcomes, measured in terms of QALYs, relative to the existing standard of care.
- By demonstrating that a new intervention offers the same health outcomes as the existing standard of care but at a lower cost.

In this study, these benefits are identified and monetised for a sample of HTA studies, and compared to the cost of the entire HTA Programme. The economic analysis estimates the direct benefits assuming all of the new interventions supported by HTA research evidence had been fully adopted, balanced against their costs. This assumption is appropriate because the role of the HTA is to provide relevant and reliable evidence for the NHS; it is beyond the remit of the HTA to ensure this evidence is used.

To make a broader assessment of the role of the HTA in entire health system it is important to consider what is known about the uptake of evidence. Some studies on the impact of HTA appraisals, such as

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<sup>3</sup> <http://www.nets.nihr.ac.uk/programmes/hta>

NICE technology appraisals, on practice suggest significant impact of HTA appraisals and others report little impact. Studies on the implementation of NICE guidance show that the extent of implementation varies by location and the type of technology assessed (Garrido et al, 2008, Ch6; Drummond, 2006). According to Drummond (2006), no health system is particularly good at the implementation of the findings from HTA appraisals.

The economic analysis in this report focuses on the benefits from adopting new interventions – there are also other ways that HTA research can provide benefits to the NHS, such as showing that current interventions are not cost effective. To assess the wider range of benefits that can be provided by HTA research, we have also conducted ten case studies. The case studies also examine the extent to which the HTA research had an impact on policy and practice.

## Economic analysis

We suspected that a few studies would have provided most of the potential benefit from the HTA programme, therefore we selected HTA studies that were judged likely to have large potential benefits to give us a baseline estimate for the impact of the programme. Studies with likely high potential benefit were identified in two ways: suggestions from NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC), and scanning of the two most recent volumes of the HTA journal. Studies were screened to ensure they met the following criteria:

- The study shows that the intervention trialled is either cost-effective or cost-saving compared to the standard of care.
- The study reports health outcomes in QALYs.
- The study shows that the probability that the intervention is either cost-effective or cost-saving is greater than 60 per cent at the £20,000 threshold for QALY value.

We identified 27 possible studies, 10 of which met the inclusion criteria. To calculate the potential benefit of the studies we assumed the recommendations were fully implemented for one year (which, were interventions are implemented, is likely to be an underestimate).

We estimate the 10 studies analysed provided a potential net-benefit of £3.0 billion based on a value of £20,000 per QALY, and £5.0bn based on a value of £30,000 per QALY. According to NETSCC, the total research cost of the HTA Programme since 1993 was £317m, with the estimated overall cost of the HTA Programme £367m. The estimated overall cost of the HTA Programme includes the cost of NHS support for HTA research.

We therefore conclude that 12 per cent of the calculated potential net benefit would cover the total cost of the HTA Programme from 1993 to 2012.

To carry out this type of analysis it is necessary to make various assumptions. The key assumptions in this study are:

- That study findings are fully implemented in the NHS, and would not have been implemented without the HTA research (as discussed above);



- There are no other benefits (or dis-benefits) resulting from other HTA studies. This is likely to underestimate the benefits of HTA research given the small size of the sample (10/743), assuming HTA studies do no harm. In particular, this excludes any studies which provide evidence for stopping ineffective treatment or treatment that is not cost effective. This assumption is examined in the case study section of the report;
- That each treatment, where implemented, is implemented for one year before it is superseded. This is likely to underestimate the impact of the programme;
- That the differences in approach to economic analysis in each study do not affect the overall estimate of impact, and that the base case scenarios from each study are good estimates;
- That results from the studies can be replicated in the general population;
- That prevalence and size of population affected has been consistent and that sources used to estimate number of cases are appropriate;
- That cost estimates provided by NETSCC are accurate;
- That the NHS budget is increased to allow for the increased costs of new interventions introduced. The analysis doesn't allow for 'opportunity cost' of other treatments displaced.

It is interesting to note that our conclusion is consistent with three studies from Canada that examine the benefits of HTA research (Jacob and Battista, 1993; Jacob and McGregor, 1997; McGregor, 2006). In these three studies, the authors model hypothetical cost reductions resulting from HTA reports. Jacob and Battista (1993) found that the cost of producing HTA reports was 7% of the projected savings from implementations of the reports' recommendations. Jacob and McGregor (1997) found that implementations of 21 HTA reports' recommendations would result in cost savings of 16-27 million Canadian dollars and McGregor (2006) found the impact of the implementation of 18 HTA studies would result in cost savings of 3.1 million Canadian dollars annually.

## Case studies

In addition to the economic analysis, ten case studies were conducted to explore the wider range of benefits that could arise from HTA research and examine some of the issues around implementation of findings. They were based on document review and interview and selected pragmatically to cover HTA studies with a high potential for impact that could illustrate and explore a range of types of potential benefits of the HTA Programme. These case studies covered four of the projects included in the economic analysis, and six other HTA projects. Across the ten case studies:

- Three had a clear impact on policy through citation on guidance, with another expected to be included in guidance that is forthcoming.
- Three showed a clear impact on practice.
- A further three cases showed some evidence of changes in practice but attributing that to the specific study is more challenging, though it is likely the study played a role.

Overall, from the ten studies, four had a clear impact on either policy or practice or both. A further five showed some evidence of impact on either policy, practice or both. In these cases, either the impact had happened but it was less clearly linked to the research, or the impact was forthcoming (e.g. the research

was expected to be included in forthcoming guidance) There was also evidence of wider impacts, such as developing the credibility of research in a particular field, or building capacity to transfer policy into practice.

We identify a number of further interesting observations from the case study set. A key observation is that it can be difficult to directly link changes in policy and practice to a single HTA-funded study (or, indeed, to any individual piece of research). Wider factors as well as other pieces of research may play an important role in both enabling and blocking implementation. This suggests that holding researchers or even the research programme as a whole, directly to account for whether particular research findings are taken up by the healthcare system is not a fair reflection of the wider environment.

This is illustrated by the role that perceptions of clinicians play in implementation. A number of the studies investigated suggested that a procedure should be removed from practice, as it costs money and does not provide any significant benefit. Here, in theory, putting the findings into practice should be straightforward since there is no 'new' treatment to introduce. However, it is challenging to overcome the existing views and habits of practitioners. In these situations, clinicians are likely used to using these interventions, and may be convinced of their effectiveness based on personal experience. They may also face pressure from industry or from patients who want to see a particular treatment used. This highlights that clinical and cost effectiveness are not always the sole driving factors in whether a new treatment is recommended or adopted – even in NICE guidance, as illustrated in at least one case study. Wider factors, including patient preference and experience, can also be important.

## Conclusions

Based on this analysis, if 12 per cent of the potential net benefit of implementing the findings of this sample of 10 studies for one year was realised, it would cover the cost of the HTA Programme from 1993 to 2012. Drawing on the case studies and the economic analysis, we have made a number of observations that could help ensure that the HTA Programme maximises the likelihood of findings being adopted:

- **Consider the full range of costs of implementation.** Conducting economic analysis to meet NICE requirements means that some types of costs are not included in most HTA studies. For example, training costs related to introducing a new intervention would not be included. Addressing these potential barriers to uptake in HTA studies could help to support implementation.
- **Consider the importance of timing relative to the revision of relevant guidelines.** There were examples from the case studies where guidance was published shortly before the HTA work was published. Communication with NICE and other guideline producers could improve timing and allow for the sharing of early results where appropriate.
- **Continue to support things other programmes are less willing to support.** Examples include long-term follow up of cohorts and meta-analyses of data across trials, both of which could support impact on policy and practice.
- **Continue to identify unproven practice in use in the NHS as well as new interventions.** There are practices used in the NHS that are not evidence-based, and where these are

ineffective, removing them could lead to cost savings. Four of the case studies illustrated how HTA research can provide the evidence about such practices.

- **Continue to require systematic reviews before primary research is commissioned.** Ensuring that primary research is only conducted where there is a gap in the evidence and that it is appropriately powered to draw the necessary conclusions, based on a review of previous evidence, will help ensure the findings of HTA-funded studies are relevant to policy and practice.
- **Improve meta-data on studies.** The HTA has an ongoing project to develop meta-data across its clinical trials (NICE HTA - 08/117/01). Gathering meta-data of this type across the HTA portfolio would enable the results of relevant HTA studies to be identified, classified and used more readily. This could promote both better analysis of the HTA Programme, and better use of its study findings.
- **Ensure consistency of economic analyses.** Several case studies showed the importance of economic analyses to the overall impact of the study. The type and quality of economic analysis included in the HTA studies differs, however, it has become more standardised over time, partly due to changing NICE requirements.

## Acknowledgements

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We are grateful to Prof. Martin Buxton and Jon Sussex for their invaluable comments and input on our economic analysis, noting that any errors that remain are our own. We would like to thank Dr Michele Mastroeni who prepared two of the case studies, and Dr Siobhán Ní Chonaill, who supported the data extraction for economic analysis. We would like to thank the team at NETSCC for their help and support, particularly Jane Robertson and Peter Davidson. We would also like to thank the Chief Investigators which we interviewed for the case studies for their time and input. Finally, thanks are due to Dr Saba Hinrichs and Dr Molly Morgan Jones for their helpful QA review of this document.

## Abbreviations

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3Mg Trial	Randomised Controlled Trial of Intravenous or Nebulised Magnesium Sulphate or Standard Therapy for Acute Severe Asthma
ARTISTIC	A Randomised Trial of Human Papillomavirus (HPV) Testing in Primary Cervical Screening
CESAR	Randomised Controlled Trial and Parallel Economic Evaluation of Conventional Ventilatory Support versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR)
DH	Department of Health
ECMO	Extracorporeal membrane oxygenation
EQ-5D	EuroQol Five Dimension Questionnaire
HTA	Health Technology Assessment
NACHBID	Neuroleptics in the Treatment of Aggressive Challenging Behaviour for People with Intellectual Disabilities: a Randomised Controlled Trial (NACHBID)
NETSCC	NIHR Evaluation, Trials and Studies Coordinating Centre
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NSC	National Screening Committee
QALY	Quality Adjusted Life year
REF2014	Research Excellence Framework 2014
SF-36	Short Form (36) Health Survey
THA-SR	Hemiarthroplasty and Total Hip Arthroplasty for Treating Primary Intracapsular Fracture of the Hip: a Systematic Review and Cost-Effectiveness Analysis
TTO	Time trade off



# 1. Introduction

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The National Institute for Health Research's (NIHR) Health Technology Assessment (HTA) programme was established in 1993 and is the largest dedicated research programme for the UK National Health Service (NHS). The Health Technology Assessment (HTA) Programme funds 'independent research about the effectiveness, costs and broader impact of healthcare treatments and tests for those who plan, provide or receive care in the NHS.' (NIHR Health Technology Assessment Programme). The purpose of the programme is to ensure that high quality research evidence is made available on the effectiveness, costs and impact of health technologies to policymakers, practitioners and patients in a timely and efficient manner. The work of the HTA Programme covers both primary research and evidence synthesis. The research is either commissioned or researcher-led. The underlying principle of the HTA Programme is that clinical research should not only use the most rigorous techniques, but should be needs-led, with a clear benefit to patients and practitioners.

HTA studies are intended to inform the key decisionmaking bodies within the health system, particularly the National Institute for Health and Clinical Excellence (NICE). As a result of this separation between the compilation of research outputs and decisions on the use of these outputs, delays (or even failures) in adoption of the techniques or guidelines recommended by researchers may occur, leading to underperformance of the health system. The Department of Health (DH) is interested in an estimate of the potential benefits that would have been available to the health system, and the wider community, if the findings of HTA studies had been implemented.

NIHR has requested this review of the impact of the HTA Programme, conducted through RAND's PRiSM (Policy Research in Science and Medicine) research unit, to assess its current performance and to consider how best to maximise its impact in the future. This is part of a wider move towards accountability amongst research funders, which reflects a growing need to demonstrate to the taxpayer and the government that public research funding is being used efficiently. This is reflected in the Research Excellence Framework 2014's (REF2014) assessment of university research, which for the first time included case studies of research impact, in addition to academic excellence, as part of the assessment (REF2014 2011). This reflects the growing consensus that research needs to be able to demonstrate wider impacts that matter to the public and that the case needs to be made to a wider audience that research is a good investment.

The importance of reflecting on research impact and the way in which research is supported is further emphasised by recent evaluations of research waste. Chalmers et al. (2014) analysed research waste in the context of priority setting and resource allocation. They made four clear recommendations, one of which

was that: ‘research funders and regulators should demand that proposals for additional primary research are justified by systematic reviews showing what is already known and increase funding for the required syntheses of existing evidence’. This is based on substantial evidence showing that researchers are not making sufficient use of existing evidence in the design and execution of their research. One study showed that of 446 trials submitted to research ethics committees in the UK, only 4 per cent used meta-analyses of data from relevant previous studies to determine necessary sample sizes (Clark et al. 2013). Similarly, an analysis of clinical trials found that less than a quarter of previous trials were cited in reports (Robinson and Goodman 2011). This failure to review existing literature prior to undertaking new research runs contrary to UK policy on research governance in the biomedical research sector. According to the DH’s framework on research governance, ‘all existing sources of evidence, especially systematic reviews, must be considered carefully before undertaking research. Research which duplicates other work unnecessarily, or which is not of sufficient quality to contribute something useful to existing knowledge, is unethical.’ (Department of Health 2005, p13). In a previous study exploring the issue of research waste, Chalmers and Glasziou (2009) describe how the HTA Programme embodies many of these principles, minimising research waste through the way that it ‘routinely requires or commissions systematic reviews before funding primary studies, publishes all research as web-accessible monographs, and, since 2006, has made all new protocols freely available.’(Chalmers and Glasziou 2009, p88)

Several attempts have been made over the years to evaluate some of the impacts of the HTA Programme. The NIHR previously commissioned an assessment of the impact of the HTA Programme (Hanney et al. 2007), which reviewed the programme’s first ten years (1993–2003) using a payback case study approach.<sup>4</sup> The study highlighted the wide range of impacts of the HTA Programme and the many ways in which these impacts can occur. The impacts primarily focused on the areas of knowledge generation, perceived policy impact, and, to some extent, on practice. The report suggests that the high impact of the HTA Programme stems partly from relevance of the work to policymakers. The high methodological standards and strict peer reviewing requirements were also thought to have helped the researchers involved in the HTA projects to publish their work in high-quality, peer-reviewed journals. The work of Hanney et al. (2007) did not include any specific economic analysis, rather taking a qualitative approach. Our work here, therefore, is complementary, and the case studies we include largely focus on more recent work that would not have been covered in that study.

Work by Raftery and Powell (2013) built on the work of Hanney et al. (2007) in their evaluation of the impact of the HTA Programme over the last 20 years. Rather than focusing on the impact of specific HTA-funded projects, as in the study by Hanney et al. (2007), their work also highlights the impact of HTA-funded research on policy and practice as well as the wider impact of the programme as a source of evidence for NICE and the National Screening Committee (NSC) and as an exemplar of good research practice. For example, the HTA Programme demonstrates good practice in terms of its full, open-access publication of results, registration of trial protocols at the outset of projects and requirement for systematic review of existing evidence before additional primary research is funded. However, the study also identified a number of key challenges for the HTA Programme. One of the key challenges identified

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<sup>4</sup> The payback framework is an approach which can be used to systematically analyse research impact and translation.



was the securing of HTA funding from the NHS in the current economic climate. Raftery and Powell (2009) argue that the programme needs to demonstrate that it is cost-effective through its impact on health service resources and wider public health. The work of our study directly responds to that need, by looking at the potential economic benefits of the HTA Programme.

The aim of this study is to demonstrate some of the economic benefits of the HTA Programme, relative to its cost. HTA-funded research can deliver economic benefits in a range of ways. In this economic analysis we focus on the benefits that can be delivered through HTA reports which demonstrate that a new intervention offers advantages over the existing standard of care. In this context, the findings can deliver benefits in two ways:

- By demonstrating that a new intervention is superior to the existing standard of care at conventional QALY values.
- By demonstrating that a new intervention offers the same or better outcomes than the existing standard of care at a lower cost.

In this study, these benefits are identified and monetised for a sample of HTA studies, and compared to the cost of the entire HTA Programme. In addition to this economic analysis, we have conducted ten case studies. The objective of the case studies is to look in detail at a wider range of impacts of HTA-funded research, which were not captured by the economic analysis. For example, one way in which the HTA Programme adds value is by showing that some interventions are not cost-effective and hence should not be introduced. The case studies highlight the extent to which the selected studies have had an impact on policy and practice.

This report details the findings of both the economic evaluation and the case studies. The report comprises the following sections:

Chapter 2: Economic analysis. Methods used and findings of the economic analysis, as well as caveats and limitations.

Chapter 3: Case studies. Description of methods used, and discussion of the overall findings across the case study set.

Chapter 4: Impact of the HTA Programme. Discussion of key findings across the whole study.



## 2. Economic Analysis

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### 2.1. Introduction

In this chapter we present the results of the economic analysis. The chapter comprises four sections: the objectives of the analysis, the methodology, the results and the discussion of the analysis. The objective of the analysis sets out the reasons for undertaking the economic analysis. The methodology section outlines the methods used for the identification of studies, data extraction and data analysis. The results section presents our estimates of the potential economic benefits of a selection of studies from the HTA Programme compares these benefits to the cost of the HTA Programme. Lastly, the discussion section provides an interpretation of the economic analysis, explores some of the challenges related to data availability and outlines the limitations of the economic evaluation.

### 2.2. Objective of the analysis

The objective of the study was to conduct an economic analysis of a sample of HTA-funded research. In essence, the analysis aims to compare the benefits that would have accrued to the NHS, if the findings of the studies had been implemented for one year, to the total cost of the HTA Programme. In the economic analysis, we focus on HTA-funded research which demonstrates that a new intervention offers advantages over the existing standard of care. In this setting, economic benefits can accrue in two ways:

1. By demonstrating that a new intervention improves health outcomes, measured in terms of QALYs, than existing standard of care.
2. By demonstrating that a new intervention offers the same health outcomes as the existing standard of care but at a lower cost.

We have chosen to focus on this type of studies in the analysis based on a set of assumptions which we have had to make in order to make the economic analysis tractable.

HTA studies are typically conducted in cases where the evidence around a particular intervention is not conclusive. Whether meta-analysis or clinical trial, they are designed to address this lack of clarity and provide conclusive evidence about the clinical and cost-effectiveness of the intervention being investigated. Therefore, it is equally likely that HTA studies will demonstrate that interventions are not better than existing care and should not be used, and this adds value by avoiding the waste of resources. However, in order to make consistent calculations around the potential economic benefit of these studies, we need to make assumptions about adoption, since good information about the level of adoption of each intervention is not readily available.

We base our analysis on the assumption that the NHS is an evidence based institution. As such, where clear evidence of the superiority of a new intervention is not available, we would expect that adoption of that intervention is minimal. Similarly, when evidence becomes available that an intervention is superior to the existing approach, we would assume it is widely adopted. Given these assumptions, along with our observation that HTA studies are typically conducted to provide some clarity in situations where there is a balance of evidence, we calculate the net potential benefit of these studies on the basis that the intervention is not in place before the study is conducted, and that it is introduced across the relevant population in the NHS once the study has been conducted. Therefore, based on our assumptions, we have to focus on those studies which demonstrate that a new intervention offers benefits over existing care, since we would assume that studies which show there is no benefit to a new intervention do not offer direct benefit to the NHS since the intervention would not have been adopted when evidence was unclear (based on these assumptions).

In reality, we understand that this is unlikely to be the case. Firstly, the HTA offers important benefits through demonstrating that practices which have been adopted should not be used, showing that implementation does not always follow clear evidence of effectiveness. Even where best practice is clearly laid out in guidelines, adoption of those guidelines can be patchy, with estimates for the level of adoption in the range of 25-59% (Audit Commission, 2005; Timmermans and Mauck, 2005; Pettit et al, 2013). Studies on the implementation of NICE guidance also show that the extent of implementation varies by location and the type of technology assessed (Garrido et al, 2008, Chapter 6). Where evidence is adopted, HTA studies may not always be critical to adoption in the way we have assumed here. Evidence on the impact of HTA appraisals, such as NICE technology appraisals, on practice is variable with some studies reporting high impact of HTA appraisals and others reporting little impact of such appraisals (Garrido et al, 2008, Chapter 6; Drummond, 2006). According to Drummond (2006), no health system is particularly good at the implementation of the findings from HTA appraisals. These issues are explored in more detail through the case studies, with recommendations made on how the HTA programme can act to maximise its impact on practice, with the caveat that much of this is outside of the control of the programme and its researchers. This recognition that adoption is outside the remit of the HTA programme is also part of the reason for the decision to use the assumptions described around the economic analysis.

As described above, considering the extent to which the findings of the HTA studies have been adopted is not within the scope of the economic analysis. The analysis also looks only at the direct benefits that would have accrued to the NHS if all of the new interventions had been fully adopted and does not consider any wider outcomes from the studies, such as further externalities on research or funding. Some of the additional benefits resulting from the HTA Programme are highlighted in the case studies.

## 2.3. Methodology

The analysis consists of three phases. First, we identified HTA studies that met our inclusion criteria. Second, we extracted relevant data to conduct the analysis. Third, we calculated the potential net benefit that would have accrued if the interventions would have been implemented and compared the net benefit thereof with the total spending on the HTA Programme since 1993.

## *Identification of studies*

The initial selection criterion was the HTA study's likelihood of having a positive potential benefit. The actual impact of the studies, in terms of impact on policy or practice, was not relevant for the sample selection at this stage. HTA studies with likely high potential benefit were screened to determine whether they met the following inclusion criteria:

- The study shows that the intervention trialled is either cost-effective or cost-saving compared to the standard of care.
- The study reports health outcomes in QALYs.
- The study shows that the Incremental Cost-Effectiveness Ratio (ICER) is below the £20,000 threshold, which was chosen to be the lower bound for cost-effectiveness.<sup>5</sup>

The identification of studies was divided into two stages. First, in a pilot stage of the evaluation the NETSCC identified an initial list of ten HTA studies, which would likely demonstrate a relatively high potential benefit in terms of either cost savings or QALYs gained. However, in the initial sample of ten studies, only three met the inclusion criteria. Note that no further exclusion criteria were applied at this stage and studies that did not meet the inclusion criteria were automatically excluded from the study sample. The main conclusion from the pilot stage was that a more comprehensive economic analysis would require a greater number of studies to be included in the final analysis.

In the second stage of the evaluation we employed two methods for identifying studies with high potential benefit. First, the NETSCC provided a further list of studies with likely high potential benefit. Second, the evaluation team scanned the most recent two volumes of the NIHR's HTA Journal to identify studies with high potential benefit. The study team has chosen the two recent volumes to ensure that studies are up to date with the most recent guidelines with regards to discounting costs and health effects and conducting a comprehensive cost-utility analysis.

As a result of these two stages of study identification, we identified 10 studies to be included in the analysis, as shown in Table 1 below. In eight of the studies the intervention was cost-effective compared to the standard of care, whereas in two of the studies the intervention was less costly than the standard of care, with no statistically significant difference in health effects compared to the standard of care.

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<sup>5</sup> The NICE guidelines recommend a £20,000–30,000 pay threshold for a QALY, based on a concept of opportunity cost of healthcare displaced elsewhere in the NHS within its fixed budget. If the ICER is below £20,000, the intervention is cost effective based on a cost per QALY threshold of £20,000. If the cost per QALY threshold is £30,000, any intervention with an ICER below £30,000 would be considered cost effective.

**Table 1 List of included studies**

Author	Title
Carroll et al. 2011	Hemiarthroplasty and total hip arthroplasty for treating primary intracapsular fracture of the hip: a systematic review and cost-effectiveness analysis
Cochrane et al. 2005	Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis
Gilbert et al. 2004	Does early magnetic resonance imaging influence management or improve outcome in patients referred to secondary care with low back pain? A pragmatic randomised controlled trial
Kitchener et al. 2009	ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening
Peek et al. 2010	Randomised controlled trial and parallel economic evaluation of conventional ventilator support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR)
Lamb et al. 2010	A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial
McCarthy et al. 2004	Supplementation of a home-based exercise programme with a class-based programme for people with osteoarthritis of the knees: a randomised controlled trial and health economic analysis
Orlando et al. 2013	Cost-effectiveness of transcatheter aortic valve implantation (TAVI) for aortic stenosis in patients who are high risk or contraindicated for surgery: a model-based economic evaluation
Pandor et al. 2013	Home telemonitoring or structured telephone support programmes after recent discharge in patients with heart failure: systematic review and economic evaluation
Vickers et al. 2004	Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis

## *Data extraction*

We extracted data from all of the studies that met our inclusion criteria. The evaluation team developed an extraction template and then extracted the relevant data from each of the studies. The extraction template comprised the following items from the base case results<sup>6</sup>:

- Prevalence of the health condition and the subset of patients with access to care.
- Treatment with corresponding standard of care.
- Incremental health effect (e.g. QALY) and incremental costs (relevant to the NHS), and if applicable the corresponding statistical significance.
- Discount rate for which costs and benefits were discounted.
- The year for which costs and benefits were calculated; estimated longevity of the health gain.
- Whether treatment was seen as cost-effective by the authors (compared to the monetised value for a QALY assumed; standard assumption in line with the NICE guidelines was £20,000 to £30,000 per QALY).
- The overall conclusions on the implications of the study of the authors.

After this initial extraction, we synthesised the data from each of the studies into a spreadsheet, in preparation for the economic analysis. The main objective of this stage was to ensure parity across all the information collected from the different trials. In this stage of the data extraction, it was also necessary to standardise the results across studies to enable cross-comparison across studies and analysis of the data. This standardisation was achieved by using the NHS Pay and Price index as a deflator to adjust the cost of the health intervention for inflation (Office of Health Economics 2014). We reported the incremental cost of each of the studies in 2012 prices, as this was the most recent information available in the NHS Pay and Price Index. No adjustment was made for the differing discount rates across the studies, as all studies with a lifetime horizon discounted both costs and benefits at 3.5 per cent, in keeping with NICE guidelines for health technology assessment (NICE 2013). Studies with shorter time horizons of one or two years did not discount either the costs or benefits. Where possible, we used the cost-effectiveness estimates reported from the NHS perspective. However, two studies reported results from the perspective of the NHS and Social Care Services while one study only reported results from the societal perspective. Including these three studies using a broader perspective has implications for the incremental cost of the intervention in our analysis.

## *Data analysis*

### Stage 1: Calculation of the net benefit

The total net benefit of the studies here is defined as the monetary benefit that would have accrued to the healthcare system if the recommendations of this selection of studies had been implemented for one year, in 2012, net of the costs of the intervention. It is likely that where interventions are implemented, they may be in place for longer than a year before they are superseded. However, we are not aware of any

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<sup>6</sup> Note: Some of the base case results included imputations of missing data whereas others were based only on the full case analysis.

robust estimates of the length of time that should be used and the estimation thereof was outside of the scope of this study. Therefore, as an alternative, we decided to look at only the benefits resulting from the intervention being implemented across the relevant population for one year as a conservative estimate for the length of time a new intervention is in use. We calculated our estimate based on the present value of the QALY stream over the lifetime of the patients who potentially could have received treatment in the one year.

It also is important to note that this definition is based on a number of assumptions: that all of the studies included in this economic evaluation are of high quality; that the studies accurately determine the health gains and the costs of the interventions in these trials; and that the trial populations are representative of the larger populations eligible for the interventions trialled.

The net benefit here is calculated based on the base case results for each study as these were assumed to be most comparable across studies. The base case reflects the model specification in the analysis with the best assumed structure, based on the best available data for the disease / health condition and corresponding patient characteristics. In order to determine the total net benefit of the studies, it is necessary to monetize the health gain from the interventions in the study. This calculation assumes that the QALYs elicited in the different trials are comparable such that a QALY gained from one intervention is equivalent to a QALY gained in another intervention. Then, under the usual assumption that the value of a QALY in the UK is £20,000 to £30,000, the net benefit per case can be calculated as follows:

$$NMB = (\text{Incremental Health Gain (QALY)} \times \text{Pay Threshold}) - \text{Incremental Cost}$$

This formula gives the product of the incremental health gain from the implementation of the interventions for one year and the pay threshold, net of the incremental cost, with health gains measured in QALYs and costs reported in 2012 prices (NICE 2013). This calculation assumed that the affected population accrues all of the benefits of the intervention after one year of implementation of the studies' recommendations. The total net benefit from implementation for one year in the United Kingdom is then the product of the net benefit per case and the total number of cases, in other words, the affected population. The size of the affected population was either: i) extracted from the studies themselves when the total number of affected individuals in the UK was reported; ii) in the cases when the studies did not report the prevalence of the condition in the UK, derived based on the prevalence rate reported in the studies using the total UK population; or iii) they were derived from high quality academic sources or systematic reviews (see Annex 2 for further details).

It should be noted that introducing a new technology might change the threshold at which patients are referred to treatment, thereby increasing the measured prevalence rate. We do not allow for the fact that prevalence is not independent of the availability and type of treatment. The calculation also does not allow for the potential displacement of other treatments. For example, if money is spent on a new intervention, over and above the cost of the intervention it is replacing (if it is replacing an existing intervention), then this means that the money is not spent on some other treatment that also may have had a positive cost effectiveness and have resulted in QALYs for a group of patients (assuming a fixed NHS budget). We do not consider this opportunity cost in our analysis of the potential benefits of the programme, in part because it is not possible to know what intervention, if any, would be displaced by the implementation of the new intervention.



## Stage 2: Calculation of the cost of the HTA Programme

The total annual costs of the HTA Programme were provided to the research team by the coordinators of the HTA Programme. No specific costing methods were adopted for this study as a full cost analysis was beyond the scope of the study. The research team assumed that the figures provided by the HTA Programme coordinators accurately reflect the total cost of the HTA Programme. Estimates provided to the research team provide an upper bound to the total estimated, which includes the costs imposed on the NHS as a result of HTA research undertaken over the period 1993 to 2013. All costs were adjusted for inflation using the GDP deflator and are reported in 2012 prices (HM Treasury 2014). The total research cost of the HTA Programme since 1993 is reported to be £317m while the overall cost of the HTA Programme may be as high as £367m. This estimated total cost of the HTA Programme includes HTA operational costs to identify, commission and monitor projects and the costs imposed on the NHS as a result of HTA research.<sup>7</sup> The costs cover all UK costs of the HTA programme.<sup>8</sup>

## Stage 3: Economic analysis

After calculating the total net benefit of the studies and the total cost of the HTA Programme, as detailed above, the research team conducted an economic analysis of the HTA Programme. The monetised benefits of the programme and the costs were compared, with all prices adjusted to 2012 prices to adjust for inflation, such that all costs and benefits are reported as net present values. The main output of the analysis is the assessment of whether the total benefits that would have accrued from the implementation of the recommendations of these studies for one year outweigh the total costs of the HTA Programme over the time period of 1993 to 2013. It is important to note that the analysis does not correspond to a full cost-benefit analysis of the HTA Programme. A full cost-benefit analysis would require data extraction from all studies funded by the HTA Programme. This analysis included a small subset of the HTA's funded studies. In addition, the analysis only included a selection of studies that showed positive outcomes: studies that demonstrated cost-effectiveness at a cost per QALY of £20,000 or cost-savings. Therefore, this analysis can only compare the benefits accrued from these so-called 'big ticket' studies with the overall cost of the programme.

## 2.4. Results

The two methods for the identification of studies resulted in the identification of 27 possible studies for inclusion. However, only 10 of these studies met the inclusion criteria and were included in the economic analysis. These 10 studies show an overall net benefit of £3.0bn at a value of £20,000 per QALY and

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<sup>7</sup> Note that the costs to the NHS takes into account infrastructure cost, including usage of NHS facilities, but also wider usage of NHS capacity with regards to staff and administrative cost.

<sup>8</sup> Prior to the creation of NIHR in 2006, the HTA programme was funded from UK sources. From 2006-2012 funding was through NIHR and so was from England only. From 2012 onwards NIHR requested a financial contribution towards research costs from the devolved nations. All costs, whether from the UK or England only, are included in this analysis, and compared to benefits based on incidence across the whole of the UK.

£5.0bn at a value of £30,000 per QALY. The net benefit resulting from these studies is an estimation of the benefit that would have accrued if the recommendations of these studies had been fully implemented in the United Kingdom in 2012, which is a hypothetical scenario. The estimate also does not allow for displacement of other treatments due to the increased cost of the new interventions.

If 12 per cent of this potential net benefit of the interventions were realised as a result of the work of the HTA programme, it would cover the full cost of the HTA Programme from 1993 to 2012. See Annex 1 for the detailed results.

## 2.5. Discussion

### *Economic returns*

The results of the economic analysis should be interpreted with caution given the considerable uncertainty surrounding many of the parameters in the modelling of the net benefit from the hypothetical implementation of the findings of this relatively small sample of HTA work. The results of this analysis should therefore be interpreted as a rough estimate of the potential economic gains to be had from funding clinical trials and the resulting economic analyses.

This evaluation only considered studies with positive economic returns that showed that an intervention was more cost-effective or cost-saving than the existing standard of care. Studies that demonstrated that the new intervention was not cost-effective were not included in the economic analysis as there is no straightforward method to assess the counterfactual of the benefits that have accrued to the health system from not implementing interventions that HTA studies have shown to be not cost-effective. Therefore, by limiting the inclusion criteria to studies that show positive returns, the net benefit, by definition, must also be positive.

### *Availability of data*

We had some difficulty identifying potential studies for inclusion as a systematic scan of all the papers published in the HTA's journal was beyond the scope of the evaluation. The two methods that were used for the identification of studies yielded a total of 27 studies for potential inclusion. Of these studies, less than half met the inclusion criteria for the study such that the total number of studies included in the economic analysis was relatively small (10 in total). The majority of the studies were excluded because they did not conduct a cost-utility analysis with QALYs as the outcome measure. Many of the studies, particularly the older studies, looked at the cost-effectiveness of different interventions using only clinical outcomes such that it was not possible to easily compare the benefit of the interventions across studies and it was not clear how one could then monetise the health gain from the intervention as the monetary value that can be placed on improvement in particular clinical symptoms is not well-established. The remaining studies were excluded because of high uncertainty regarding the health gain of the intervention. We chose a cut-off of 60 per cent probability that the intervention is cost-effective at £20,000 in the net benefit analysis.

After the initial identification of the studies, the data for the economic analysis were relatively straightforward to extract. All of the included studies reported on: the perspective of the analysis; the

incremental QALYs gained; the time horizon of the benefit; the incremental cost of the intervention; the price year of the analysis; and the discount rate. However, information on the prevalence of the condition being targeted by the intervention and information on the total number of people potentially eligible for the intervention was difficult to extract from the studies. Where the prevalence rate was reported by age or gender but not the number of individuals affected, the total number of cases in the UK was assumed to be the sum of the total UK population within the particular demographic group. Where no estimate of the prevalence of the condition was given, the prevalence rate was estimated from high-quality academic sources and systematic reviews. Nevertheless, it was not always possible to determine the precise number of individuals eligible for the intervention. The total number of individuals treated for each of the studies should thus be interpreted as an estimate of the plausible number of individuals eligible for the intervention.

An assessment of the quality was not included in the economic analysis as it was beyond the scope of our analysis. HTA studies were included in the analysis as long as they met the inclusion criteria. As a result, an important assumption of the economic analysis is that all of the studies that met the minimum inclusion criteria were of high methodological quality in terms of the application of best practice cost-effectiveness methods. However, the research team did note that the cost-effectiveness methodology for some of the older studies from the early 2000s differed somewhat from the methodology adopted by the more recent studies. This is perhaps not surprising as the methods for cost-effectiveness have changed over time, as is evidenced by NICE's periodic revision of the guidelines. Some of the challenges related to the identification of studies that met all of the inclusion criteria may have stemmed from developments in the best practice for cost-effectiveness methods.

This assumption of quality is also related to the wider assumption that HTA studies at least do no harm. As we are looking at a sample of studies, and comparing the sample to the full cost of the whole programme, we assume that this means that the benefits, if analysed across the whole programme, would be greater than those found in our economic analysis. However, this assumption implies that no harm is caused by the studies. This is a reflection of an assumption of quality of the work. We assume for example, that there are not any studies in the programme which indicate a treatment should be implemented which is in fact harmful.

### *Limitations*

There are a number of important limitations to this economic evaluation. This section will outline these limitations, their source, and their impact on the outcomes of the economic analysis presented in the previous section. A summary is provided in Box 1.

First, the study included a relatively small sample of studies from the HTA Programme. Our analysis included 10 studies. To put this number into perspective, the NIHR's *HTA Journal* comprises 18 volumes with 743 reports. A full economic evaluation of the HTA Programme would need to consider the costs and benefits of the entire HTA Programme, rather than small sample of the research funded. On the other hand, the large estimated potential economic returns to these 10 studies exceed the total cost of the HTA Programme. If even a small fraction of the remaining HTA-funded studies yield similar returns then it may be that the HTA Programme is even more cost-effective than is suggested by this analysis.

Second, the studies included in the economic analysis each address different clinical conditions and employ different methods for economic evaluation. For example, two studies conducted the cost-effectiveness evaluation from the NHS and Social Services perspective and one study used the societal perspective, while the remaining eight studies reported the results from the perspective of the NHS. Our

**Box 1. Summary of limitations**

- Small sample size (10/743).
- Aggregates economic analysis from different studies which use different approaches
- Uses base case results from each study only - no consideration of range of results from each study.
- Total number of cases not always provided in studies and derived from a range of sources with assumptions around prevalence and size of population affected required
- Assumes each intervention implemented for one year before superseded
- No formal cost estimate of the HTA programme – based on estimates provided.
- Assumes that results from the studies can be replicated in the general population.
- Only looks at benefits of HTA programme which result from the identification of new treatments that are more cost-effective or cost-saving.
- Doesn't allow for 'opportunity cost' of other treatments displaced
- Value of net potential benefits assumes the findings are fully implemented in the NHS, and would not have been without the relevant HTA study.

analysis used the results from the NHS perspective wherever possible but for these three exceptions used the results from the only perspectives given. The impact of including these three studies that use a broader perspective on our analysis is that a portion of the net benefit calculated actually accrues to society and the social care system rather than exclusively to the NHS. The studies also differed in their approach to QALY elicitation. The majority of studies used the EQ-5D for QALY elicitation or derived the utility estimates from a literature review of existing quality-of-life studies whereas one study used the SF-36 elicitation method. No adjustment was made for the different QALY elicitation methods used in the studies. It is unclear whether the net impact of the different methods employed will have resulted in an overestimation or underestimation of the benefits, given the variety of different methods employed.

Third, this study used the base case analysis rather than numerous potential alternative results presented in the sensitivity analyses. The base

case was used in the analysis as it was considered to be most comparable across studies. However, an important limitation of this approach is that evaluation of the robustness of the studies is not included in the base case analysis such that the base case results may not accurately demonstrate the true benefits of the intervention. For example, the base case analyses do not include imputations of missing data, which may result in biased results to differing extents, depending on whether the cost or quality-of-life data was missing at random, missing completely at random, or not missing at random. However, the impact of the

treatment of missing data within each of the studies was not within the scope of our analysis, thus the impact on our findings is uncertain.

Fourth, an important limitation of the study was the derivation of the total number of cases. Most of the studies included in the analysis did not provide an estimate of the total number of individuals in the UK with a particular condition. The prevalence of the condition could be extracted from a number of studies and then coupled with the population estimates in the relevant demographic group from the most recent census in the United Kingdom. However, this calculation may have introduced some uncertainty into the analysis as the prevalence of the condition may have changed over time, and our approach used the reported prevalence from the different studies that took place in different years and derived the total population based on 2011 population estimates. In some cases, neither the prevalence nor the size of the population affected was given in the study, in which case it was necessary to review the published literature to derive estimates of the total number of individuals at-risk for the intervention. This third method of deriving prevalence estimates likely introduced the greatest uncertainty as it is not possible to determine whether our estimates of the population affected match those which the interventions targeted.

Fifth, the analysis assumed that all of the benefits of the interventions accrued after only one year of implementation of the interventions. This leads to the fact that the estimated net benefit is likely an underestimate of the true potential net benefit of the interventions because the interventions, if implemented, are likely to be used for more than one year. For the purpose of this analysis we monetise the present value of the reported QALY stream over the lifetime (or shorter time horizon for studies that did not reported lifetime QALYs) of the patients who potentially could have received treatment in the one year. Therefore, the net benefit may be greater than suggested by our economic analysis because more individuals could potentially benefit from the implementation of these interventions in subsequent years. However, a longer period of implementation was not considered as at the time of writing this report, we were not aware of any robust estimates of the length of time that a particular intervention is used before it is replaced with a superior intervention. The above economic analysis only considered the benefits resulting from implementation of the interventions across the relevant population for one year as an alternative to trying to address this complex issue which is outside the scope of the study analysis.

Sixth, the total cost estimates of the HTA Programme are uncertain. Estimates of the research costs were provided by the HTA Programme. The additional costs of the HTA Programme were also provided and suggest that the total programme costs may be as high as £367m, which includes the operational cost of the programme and the imposed costs on the NHS from HTA-funded research. There is some uncertainty around the actual costs imposed to the NHS from HTA research, and a baseline assumption as a percentage of funding costs was used. However, this uncertainty surrounding the cost estimates was not thought to be a major limitation of the study as the even if the costs of the HTA Programme were substantially greater, only a relatively small proportion of the potential net benefits from the implementation of the interventions would need to be realised in order to outweigh the costs of the HTA Programme.

Seventh, the economic analysis assumes that the results deriving from the clinical trials can be replicated within the general population. However, it is likely that this assumption will not hold as the population recruited for clinical trials is often not fully representative of the general population with the targeted

condition and the treatment received within trial in both the intervention and control groups is often not the same as the treatment given outside the care in terms of attention given and length of follow-up.

Eighth, the economic analysis assumes that the benefits of the HTA Programme result solely from the identification of new treatments that are more cost-effective or cost-saving. However, the HTA Programme may result in many additional benefits, which cannot be captured through the type of economic analysis outline above. For example, several HTA studies indicate that a treatment or practice is not cost-effective, and should be discontinued. Although the economic analysis could not address these kinds of impacts, the case studies presented in Chapter 3 illustrate some of the broader impacts of the HTA Programme. HTA studies may also reach a final conclusion on a topic, or draw a line under a particular question or area of debate, by conducting a meta-analysis of data, or by conducting an appropriately powered trial, which likely results in a more efficient allocation of research funds. The HTA Programme may also offer wider, more intangible benefits, by acting as an exemplar of good practice through behaviours such as requiring systematic review evidence before commissioning a trial, or publication of trial protocols, influencing the behaviour of other funders.

Ninth, the analysis does not allow for the potential displacement of other treatments. As described previously, when money is spent on a new intervention, over and above the cost of the intervention it is replacing (if it is replacing an existing intervention), given a fixed NHS budget this reduces the money available to spend on other treatments that also may have had a positive cost effectiveness and have resulted in QALYs for a group of patients (assuming a fixed NHS budget). This opportunity cost is not included in our analysis of the potential benefits of the programme, in part because it is not possible to know what intervention, if any, would be displaced by the implementation of the new intervention.

Finally, the estimate of net potential benefit from the studies assumes that the findings of the work supported through the HTA Programme are fully implemented in the NHS, and indeed that the new interventions tested had not yet been implemented before this study was conducted, and would not have been implemented without this study. The rationale for this assumption is laid out in section 2.2 and is based on the underlying assumptions that the NHS is an evidence based organisation and that HTA studies are conducted where the balance of evidence on an intervention is unclear. The approach also reflects the fact that implementation of the findings of research funded by the HTA is outside the control of the HTA. However, it is possible that the way in which HTA studies are conducted and their communication and dissemination by their authors and the programme more widely are likely to impact on the extent to which the studies' findings are taken up. Despite this, the wider context and other work in the field will almost certainly play a role in the extent to which findings are adopted. These assumptions around implementation are likely to be unrealistic in practice. As a result, in our analysis we consider the percentage of the potential net benefit that would need to be achieved to match the costs of the programme. This recognises the fact that only a proportion of these benefits will be seen. However, it should also be borne in mind that this only covers a sample of projects, and indeed does not include studies which show that existing practice can be discontinued which can offer significant potential costs savings. These are some of the most difficult assumptions underlying the analysis conducted here and as such these issues are explored through the case studies described in the next chapter.

## 3. Case Studies

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### 3.1. Introduction

In addition to the economic analysis, we conducted ten case studies. These are separate from the studies identified in the economic analysis, although there is some overlap. In this chapter we present the findings of those ten case studies. The chapter comprises four sections: the introduction, the objective of the analysis, the methodology and the observations and discussion. The objective section sets out the reasons for conducting case studies as a complementary evaluation technique to the economic analysis. The methodology section details the methods employed for the selection of the case studies and the data collection tools used to conduct the case studies. The observations and discussion sections synthesises the results of the case studies and highlights the main findings of the case studies in terms of their wider impacts. The full text of all ten case studies is provided as Annex 3.

### 3.2. Objective of the analysis

The aim of the case studies was to determine the wider impacts of a set of projects with a high potential for high impact. In particular, we sought to determine the extent to which the findings of the studies have had an impact on policy and practice. This is in order to explore some of the assumptions around adoption made in the economic analysis. Another main objective of the case studies was to highlight some of the types of benefits resulting from the studies that were not captured through the economic analysis.

### 3.3. Methodology

As described above, the aim of the case studies was to look at the wider impacts of a set of projects which were felt to have a high potential for impact to understand the extent of implementation and the range of impact observed. As such, the case studies were selected pragmatically to reflect these needs. We also wanted to include a number of the studies used in our economic analysis in the case study set so that we could provide some context around our quantitative work and potentially improve, or at least better interpret, the findings of that analysis.

The case studies were selected in discussion with NETSCC, drawing on their knowledge of the HTA portfolio, to identify interesting HTA studies that had high potential to impact on policy, practice, and ultimately health outcomes and economic benefits, taking in some of the studies that had been included in our economic analysis. We also wanted to take in case studies that demonstrated other types of benefits

that are not captured through the economic analysis. One particular important group here which was highlighted to us by NETSCC, are studies which show that interventions which are in use or being considered for use are not cost-effective and should not be used. Therefore, we also tried to include some studies which fell into this category. The final selection of studies is shown in Table 2 below.

**Table 2 Final selection of case studies**

Volume and Issue in HTA journal	Title of study	Included in our economic analysis?	Demonstrates that an intervention is not cost-effective?	Year of publication in HTA journal
14/35	CESAR: Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure	√		2010
15/36	THA-SR: Hemiarthroplasty and total hip arthroplasty for treating primary intracapsular fracture of the hip: a systematic review and cost-effectiveness analysis	√		2011
13/51	ARTISTIC-2: A randomised trial of human papillomavirus (HPV) testing in primary cervical screening	√		2009
17/10	The CRASH-2 trial: A randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients			2013
8/48	Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis	√		2004
TBC	3MG: Intravenous or Nebulised Magnesium Sulphate Versus Standard Therapy for Severe Acute Asthma		√	2014
16/9	The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy			2012
13/21	NACHBID: Neuroleptics in the Treatment of Aggressive Challenging Behaviour for People with Intellectual Disabilities		√	2009
10/29	PAC-Man: An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial		√	2006
13/15	DIGEM: Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial		√	2009



For each case study, data was collected based on document review and interviews with a member of the team involved in the HTA study. The aim of the document review was to look at the level of adoption of the study findings, and the evidence available around the topic before the HTA study and following it. As such, we reviewed the relevant HTA publication and related journal articles; systematic reviews and NICE (and where appropriate, other) guidance on the topic, if available; the project website; and publications regarding other closely related studies, if appropriate. For all but one of the studies,<sup>9</sup> we interviewed the chief investigator for that study. Interviews were semi-structured based on a protocol which focused on four key themes: details about the study (cost, dates, publication, intervention tested and control); the context in which the research was conducted, including the motivation for the study; the key findings of the study and their potential implications; and the impact of the work (citation in systematic reviews or guidelines, adoption into practice, etc.). The interviews typically took one hour and were conducted by telephone.

The case studies were written up using a standard reporting template to aid comparability and ensure data collection for all case studies covered key main points. Although the template was standardised, case studies were allowed to vary in length to reflect the difference in complexity between studies, the varying amount of prior work and important context that needs to be explained, and the differences in range and extent of impacts between studies. The template for reporting largely reflects the themes identified in the interview protocol, and has the following four sections:

- **Description of the study.** Outline of the intervention tested, and how it differs from standard of care, description of the relevant condition treated if necessary, costs and dates of study, list of the reports published on the study.
- **Context.** Description of the situation before the work was conducted regarding the implementation of the new intervention (UK focus, but including information on wider implementation if interesting and relevant), the available evidence regarding the intervention, ongoing research and funding for research in that area, and the overall impetus for the work.
- **Findings of the study.** Description of the key findings of the study in terms of the effectiveness and cost effectiveness of the new intervention compared to standard of care, description of the potential population addressed, qualitative/quantitative description of the potential benefits or dis-benefits of the new intervention over standard of care, and any challenges that might impede implementation, or factors that might facilitate adoption.
- **Impact.** Description of the impacts of the study on policy and practice and how this impact came about, quantification, where possible, of the extent of implementation and the benefits of this, qualitative description where this cannot be quantified, and if the impact is limited, discussion of the reasons for this, comments on the potential for future impact of the work.

The listed content reflects the information we have aimed to capture for each case study. In some cases, some of this information is not readily available, and is therefore not included. However, we have attempted to cover these key issues in each case study where possible.

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<sup>9</sup> Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.

### 3.4. Observations and discussion

Given both the limited size of the sample set, and the pragmatic selection of case studies, it is not possible to draw any firm conclusions about the extent to which HTA findings are implemented, or the importance of different factors in the impact of HTA studies. However, it is possible to identify interesting observations and themes emerging across the ten case studies which help to provide some context around how and why HTA findings might, or might not, be taken into account in policy and practice, and the importance of HTA work in the context in which it is conducted. These observations, given the number and selection of case studies, are not suitable to modify the economic analysis. They may, however, provide some context around those findings and their analysis. In addition, a summary of the impacts observed in each case study is provided as a table in Chapter 4.

#### *Effect of timing of study on its impact on policy and practice*

One observation which is relevant to a number of case studies is the importance of timing relative to the revision of relevant guidelines. There are several cases where NICE guidelines have not been updated since the study was completed and hence the work has not had an impact on the guidance provided. In some cases, guidance was published shortly before the HTA work was published. There may be an opportunity to improve this situation by communicating with relevant guideline committees and perhaps providing pre-publication findings for them to take into account where relevant. This illustrates the potential importance of timing of the study to the impact it has. For example, the THA-SR study involved a scoping stage, followed by a full review. However, before the study was complete, another systematic review had been conducted which was published in the *BMJ*, and the relevant NICE guidance had been revised. Although the HTA study was perhaps more rigorous (or at least narrower in its criteria for inclusion) than the study published in the *BMJ*, because of its timing it was less important in terms of the impact it has on policy.

#### *Attribution of impacts to the HTA-funded study*

This raises another issue, which is the extent to which changes in policy and practice can be attributed to the HTA-funded study (or, indeed, to any individual piece of research). The PAC-Man study took some time from the initial consensus process to the work starting and thus by the time the trial actually commenced, pulmonary artery catheter (PAC) use was already in decline. So although it was still important in providing robust evidence that PACs were ineffective, it was actually less robust evidence which suggested (arguably incorrectly) that PACs might be dangerous which started their decline in use, though the PAC-Man study also played a role in this.

Several of the case studies provide examples of this situation. Looking at the CESAR study, it is not clear how far the research of the study contributed to the development of ECMO centres, when compared to the importance of the spread of the H1N1 virus. Considering the ARTISTIC study, its coincidence with the introduction of HPV vaccination is perhaps unsurprising, but with vaccination decreasing the need for screening and hence screening costs, its importance in possibly making screening more cost-effective is diminished. This is a subtly different case. The presence of other factors, namely the growth in HPV vaccination, doesn't call into question the role of the study in changing the screening process; rather it

diminishes the importance of that change. The issue therefore is not attribution of the change to the study; it is, rather, the role of external factors, outside the control of the study team, in determining the extent to which the study contributed to the NHS.

This raises an important point. Although we consider the context in which the study concept was developed in each of the case studies, the studies typically take several years, due simply to their nature, and that the work is conducted in a changing environment. Other research, changes in healthcare systems and structures, changes in the health of the population and other wider environmental factors can mean a study which was clearly needed when commenced may have less relevance or value once completed. This is not a criticism of the HTA Programme (or any other such research programme) – and, indeed, these cases studies show how robust evidence can still provide a valuable contribution in a changing environment. However, it does indicate that holding researchers or even the research programme as a whole, directly to account for the extent to which individual pieces of research are taken up by the healthcare system does not reflect the environment in which they are operating.

### *Feasibility of implementing study findings*

However, it is relevant to consider characteristics of each study, or of the wider research and policy system, which may limit the applicability of research to practical NHS use. One such factor is the extent to which implementation of findings is truly feasible in the NHS context, and the way costs are taken into account. Conducting economic analysis to meet NICE requirements means that some types of costs are not included in most HTA studies. Although studies cover NHS costs, they only cover the costs of the intervention in practice. Typically, some of the costs and challenges involved in introducing a new intervention are not considered in the economic analysis, though some authors will mention them in the wider discussion. A clear example of this is the necessary training and/or experience needed to put an intervention into practice. This is illustrated in the THA-SR study. Here, total hip arthroplasty (THA) is recommended over hemiarthroplasty (HA), with the improved quality of life meaning this procedure is more cost effective. However, the procedure is less straightforward to carry out and is typically only performed by more experienced clinicians. Therefore, implementing this in the NHS will either mean that costs which have not been accounted for will be incurred in training additional people to be able to perform this type of surgery, or it will mean that waiting times for procedures will likely increase as a more limited number of clinicians is able to carry out the necessary procedure, which will have quality of life implications that have not been accounted for. Similarly in the case of the EVAR study, the new procedure, EVAR, is known to fewer clinicians than standard of care (open repair) and the team suggested that around 40–50 procedures are needed before a practitioner becomes suitably adept at the process. They suggest that the increasing concentration of this type of procedure in specialist centres reduces this problem, but nonetheless, there are training implications that are not accounted for in the economic analysis.

### *The role of other stakeholder groups (clinicians, industry and patients) in implementation*

In contrast, there are a number of studies where the findings suggest that a procedure should be removed from practice as it is costly and does not provide any significant benefit (as seen in the PAC-Man,

DiGEM and 3MG studies). Here, putting the findings into practice should be easy in principle. However, the challenge is overcoming the existing views and habits of practitioners. In these situations, clinicians are familiar with using these interventions, and may be convinced of their effectiveness based on personal experience, or may face pressure from patients who want to see a particular treatment used. In this context, even where clear evidence is available that a treatment offers no benefits and is effectively a waste of money, if there is no direct evidence of harm resulting from the treatment, it can be difficult to change practice, and it will take time and effort to educate clinicians. This perhaps reflects the limited involvement of some groups of clinicians in research. A recent survey, for example, found that although 87 per cent of medical professionals believe that it is important for the NHS to support research, only 46 per cent of medical professionals feel they have a duty to be personally involved in research, which falls to 22 per cent amongst GPs (AMRC 2013). Lack of involvement in research may lead to a poorer understanding of research and limit the ability to take up research findings and use them in practice.

Industry also plays a role in the development of the research agenda. In the case of EVAR, the commercial development of products to support this procedure was one of the factors that contributed to the identification of this topic as important to study to test the safety of the procedure. Several researchers, at interview, cited industry lobbying (through direct contact with practitioners or through the publication of unreliable 'systematic' reviews waiting the evidence in their favour) as blockers to the implementation of research findings. More than one interviewee stated that they had received personal negative attention from industry representatives or lobbying groups.

Patient groups also play a role in the extent to which research findings are taken up. Clinical and cost-effectiveness are not always the sole driving factors in whether a new treatment is recommended or adopted – even in NICE guidance. For example although EVAR was not shown to be cost effective relative to open repair, use of the technique has still increased because it is preferred by patients (because it is less painful, the operation is under local anaesthetic and can almost be carried out as an outpatient procedure, etc.). However, the trial evidence was still important as it confirmed that the procedure was safe over the mid to longer term (with longer term results still forthcoming). This is also seen in some of the statements in guidance regarding self-monitoring of blood glucose. Although the DiGEM study provided clear evidence that it is not cost-effective, IDF guidance still suggested that it could be used, with some caveats (International Diabetes Federation, 2009). This is likely to be partly because of patient lobby groups, who do not want to see treatments 'taken away' from them. There is some expectation that similar caveats will be seen in guidance relevant to the findings of the 3MG study.

### *Existing NHS practice which is not supported by evidence*

Although it can be debated whether patient perceptions should influence clinical guidance, counter to the research evidence, what is more clear is the problems created by practice which is introduced based on little or no research evidence. Despite an increasing focus in the NHS on becoming an evidence-based organisation, there is clear evidence that there are still practices being used without evidence of their effectiveness. In the case of DiGEM, the usefulness of a treatment was extrapolated from a related condition: self-monitoring of blood glucose has some evidence of usefulness (or at least a clear rationale for usefulness) in the case of patients with Type 1 diabetes who are using insulin to regulate their blood glucose. Its utility for Type 2 diabetes sufferers who are not regularly using insulin is less clear, but

nonetheless this usefulness seems to have been extrapolated, perhaps with the help of industry, such that it became widely used in this context. PACs are a different case: a 'legacy' practice which had never been tested but continued to be used without an evidence base. In the case of the 3MG study, the effectiveness of magnesium sulphate appears to have been extrapolated from a limited evidence based, and for NACHBID, a gap in evidence had been filled by industry-funded trials, supporting the use of antipsychotics. It is interesting to note that in all these cases, the evidence of the studies did not show any significant harm (or benefit) from the interventions tested (with the possible exception of side effects of these treatments, notable in the case of the antipsychotics used in the case of NACHBID) at least on the basis of their primary outcomes measures. Rather, they showed that the interventions offered no benefit and cost savings could result if they were discontinued.

This observation has implications for the assumptions underlying our economic analysis. Clearly, not all practice in the NHS is based on existing clear evidence of its validity, and as such our assumption in the calculation of net potential benefit that adoption will not occur without appropriate evidence is likely to be incorrect. As such, it is important that we consider the economic result in terms of the proportion of the benefit that would need to be observed to justify the costs of programme. We can still assume that adoption increases where evidence of effectiveness is provided, and this is shown in the case studies. For example, in the CRASH-2 case study, we see a significant increase in the level of use of TXA in trauma patients (estimated at 75%, compared to very low levels of usage previously), and in the CESAR case study, the number of ECMO centres grew from one to five, with the number of intensive care beds doubling over a short period during that process, to 190.

### *Impact on further research*

Another interesting theme that emerges from the case studies is the role that the studies played in developing the research field in which they were conducted. The PAC-Man study is an example of this. As one of the first RCTs in critical care medicine in the UK it was a landmark study and paved the way for further such studies in the field. Similarly, the NACHBID study was important in showing that evidence can be provided in the field of intellectual disability where the existing evidence base was poor, in part due to the challenges of recruiting patients with intellectual disability into trials. In fields where research is less established, there is often little official guidance, from NICE or other sources, around practice and as such other routes to dissemination are needed. Two of the studies here provided examples where networks, either existing or developed through the study, were important in the dissemination of findings into practice. In the PAC-Man study, the network that the researchers had through their dual role as both auditors and researchers meant that they could directly access critical care units across the UK and they disseminated their findings directly to practitioners. In the CRASH-2 study, networks were important at two stages in the dissemination of the work. In the early stages, the findings were put into practice rapidly in a military context partly due to pre-publication results being shared with the relevant people, showing networks and contacts that were in place. Later, dissemination into wider civilian practice was facilitated by the UK trauma network. NACHBID provides an alternative route, where the trial, together with a few other studies ongoing at the time, collectively resulted in the creation of a NICE project team to on challenging behaviour and learning disabilities, which is now working to produce guidance in the area.

In two of the studies, members of the project team went on to synthesise evidence across multiple trials, when the evidence of the trial they had conducted was not able to provide the detailed information they needed, or wasn't sufficient to influence practice in the way they had hoped. For the EVAR study, the aim of the ongoing meta-analysis is to look in more detail at when and how complications occur to try and understand how the risk of complications can be minimised. In the DiGEM study, meta-analysis strengthened their case that self-monitoring of blood glucose offered no significant benefit, and also allowed them to demonstrate this for specific patient groups as well as across the population in general.

### *Diversity of approaches to topic identification*

There is no evidence from this set of case studies that the way in which the topic is identified influences the impact of the project. A wider systematic analysis across the portfolio would be needed to draw this type of conclusion. What we can say is that the sample here illustrates that there are a diverse set of processes that lead to the development of an HTA project. This can be through the findings of a prior systematic review (e.g. DiGEM, 3MG), or through a consensus process (PAC-Man). The topic can be identified by the HTA Programme (ARTISTIC, THA-SR), or the idea can be sparked by the individual experiences of a particular CI (e.g. CRASH-2).

## 4. Impact of the HTA Programme

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### 4.1. Overview of the impact

Across the 10 studies used in the economic analysis, we identified an overall potential net-benefit of £3.0bn based on a value of £20,000 per QALY and £5.0bn based on a value of £30,000 per QALY. This is an estimation of the benefit that would have accrued if the recommendations of these studies had been fully implemented in the United Kingdom in 2012 for one year. The total research cost of the HTA Programme since 1993 is reported to be £317m while the overall cost of the HTA Programme may be as high as £367m (including NHS costs). Together, this suggests that if 12 per cent of the net benefit of the implementation of the findings of these ten studies for one year was realised, this would cover the total cost of the whole HTA Programme from 1993 to 2012, implying the HTA Programme is likely to offer a positive return on investment, considering that this is a small sample of the programme's work.

In many ways, this is a conservative estimate of the economic benefit of the HTA Programme. It is based on a relatively small sample of studies from the HTA Programme (10 out of over 700 HTA studies). If even a small fraction of the remaining HTA-funded studies yield similar returns then it may be that the HTA Programme is even more cost-effective than is suggested by this analysis. Although many studies will not demonstrate a new cost-effective treatment in this way, a lot will also provide value in a different way, such as by showing that a treatment is ineffective and should be stopped, or by better directing future research so research funding is not wasted. Furthermore, it is likely that where interventions are implemented, they will be in place for longer than a year, meaning a larger population will benefit from the new intervention than is suggested by this analysis. However, the length of time for which an intervention will be in use is challenging to estimate. A longitudinal analysis of clinical guidelines might reveal the length of time between treatments being recommended and being subsequently superseded. Even if this value were available, however, it is likely that there would be a significant variance on this value, and even then citation on guidelines does not always correspond to what happens in practice, and speed of uptake of guidance may vary over time and between fields. Where possible, most other criteria used for estimation have been conservative.

### 4.2. Discussion of the impact

The findings of this study are consistent with three studies from Canada that show that HTA reports likely result in cost reductions (Jacob and Battista, 1993; Jacob and McGregor, 1997; McGregor, 2006). In these three studies, the authors model hypothetical cost reductions resulting from HTA reports. Jacob

and Battista (1993) found that the cost of producing HTA reports was 7% of the projected savings from implementations of the reports' recommendations. Jacob and McGregor (1997) found that implementations of 21 HTA reports' recommendations would result in cost savings of 16-27 million Canadian dollars and McGregor (2006) found the impact of the implementation of 18 HTA studies would result in cost savings of 3.1 million Canadian dollars annually.

However, to make conclusions on whether the HTA programme truly is cost effective, we need to understand the extent to which the findings of these studies are implemented, and the role that the HTA programme plays in that implementation. It should be noted that, to some extent, this is outside the remit of the HTA programme itself. Research and implementation functions are separated and as such the HTA Programme cannot be held responsible for the extent to which findings are implemented, though there may be actions that the programme and its researchers could take to help promote implementation as discussed in Chapter 3.

According to the WHO (2011), there are three distinct components to the introduction and use of health technology: health technology assessment, regulation and management. The HTA Programme is involved in the first of these three components but has little or no involvement with regulation, which concerns the safety and efficacy of the technology as well as any intended or unintended consequences from the implementation of the health technology. It also does not get involved with management, which concerns the procurement and maintenance of the technology throughout implementation. In fact, according to the WHO (2011), "very close links between regulation and HTA on a country level will lead to a very superficial use of HTA not conducive to evidence-informed decision-making." Introducing new technologies requires additional resources, both financial and human, or the redistribution of existing resources within the health system (Garrido et al, 2008). This is one of the challenges in the implementation of findings from HTA studies that demonstrate the effectiveness of a new technology. The estimate of the potential net benefit from a sample of HTA research calculated in this study assumes that the conclusions and recommendations of the studies are fully implemented, even though there is not a clear mechanism in place for the HTA Programme's research findings to be directly translated into clinical practice.

The process by which an HTA report can have an impact on clinical practice has a number of different stages. For example, Garrido et al (2008) outline six steps to the impact of HTA reports:

1. *Awareness*: Policy-makers must view health technology assessment as a relevant component in the decision-making process.
2. *Acceptance*: The report is viewed as valid, relevant, applicable and the findings acceptable.
3. *Policy process*: The policy-making process explicitly uses the HTA report.
4. *Policy decision*: Any actual policy decisions take into account, and are influenced by, the report's conclusions.
5. *Clinical practice implementation*: A decision has to actually be implemented through clear changes in clinical practice.
6. *Clinical practice measurement*: Clinical practice must actually change for it to be possible to measure the impact of a health technology assessment in either health or economic outcomes.



It is, however, possible for HTA reports to directly influence clinical practice, as we explore in the case studies, which would result in the third and fourth steps being bypassed (the policy process and the policy decision).

The economic portion of this analysis assumes that the conclusions or recommendations of the HTA reports that were included in the economic analysis either a) successfully transition through the six steps of the impact process or b) bypass the policy process through the latter route just described, to deliver the returns estimated in the HTA reports. However, as outlined, there are a number of steps involved in the translation of research into clinical practice that enable the implementation of the research findings. Our estimate of the potential net benefit actually covers the potential benefits of this entire process, of which the HTA Programme is an important, but still only one, component. Evidence from the literature indicates that implementation of HTA research is variable by both technology and geographical area. In a review of seventeen studies that looked at the impact of health technology assessment on clinical practice, most of which investigated the impact of NICE guidance, Garrido et al. (2008) found that the results were variable with some attributing significant impact to NICE appraisals and others finding little impact. They also found that implementation of NICE appraisals may vary by region or by the type of technology (e.g. medical devices vs. pharmaceuticals). The Garrido et al. (2008) review also notes that,

*“the impact (positive or negative) of an HTA report depends on many factors. These can be structured into contextual factors that act independently of a specific HTA; factors related to process around an HTA report; those concerning the content, quality of format of the reports; and those related to the technologies.” (p112-113)*

While an evaluation of the actual impact of specific HTA reports was beyond the scope of this study, it is important to note that there are many mitigating factors that would determine whether the studies included in the economic analysis could actually deliver the estimated returns.

Based on the translation steps described above, to understand the extent to which the calculated potential net benefits would be realised, we would need to understand three things:

1. What proportion of HTA research has an impact on guidelines?
2. To what extent are those guidelines implemented in practice?
3. What proportion of HTA research has a direct impact on practice (i.e. not via guidelines)?

There is some information on the second of these questions available in the literature. In 2005, the Audit Commission found that 25% of NHS bodies could verify that NICE technology appraisals had been implemented within three months of publication, with lower, but highly variable, rates for clinical guidelines. (Audit Commission, 2005). Analysis of the ‘evaluation and review of NICE implementation and evidence’ (ERNIE) database by Pettit et al (2013) suggests that for 59% of clinical guidance, practice appears to be in line with guidance (in the UK NHS). Internationally, the picture is similarly variable. A meta-analysis of adherence to clinical guidelines in the US found a mean adherence rate of 54.5 percent (Burstin et al., 1999). A study conducted in the Netherlands found that guidelines were followed about 67 per cent of the time (Grol, 2001).

Information on the first and third questions is more sparse. Garrido et al. (2008) reviewed 14 studies internationally that looked at the impact of HTA research on policy. They conclude that the majority of

these studies found at least 70% of HTAs to have impacted on policy, but that some found the impact highly variable and the quality of the studies was mixed. Recent work by Wright et al (2014) suggests that work funded by the HTA programme is typically clinically relevant, which suggests that HTA research may be relevant to practice but doesn't give us any clear information on the extent to which it is taken up. HTA studies can also have impact above and beyond their impact on clinical practice. For example, a review by Garrido et al. (2008) found that, "HTA was using to identify gaps in applications, support decisions on appeals, define adequate patient-centred outcomes and create research questions." For example, HTA studies are typically commissioned where the evidence on a particular intervention is unclear and further information is required to clarify whether it is clinically and cost effective. In this context, we might expect that HTA-funded research plays an important role in the decision whether to implement a particular health technology. We explored this through the case studies.

### 4.3. Evidence from the case studies

Analysis of the 10 case studies, focusing on HTA projects with a high potential for impact, is presented in Table 3. This analysis shows across the set of ten case studies, three had a clear impact on policy through citation on guidance, with another expected to be included in guidance that is forthcoming. Three showed a clear impact on practice, and in a further three cases there is some evidence of changes in practice but attributing that to the specific study is more challenging, though it is likely the study played a role. Overall, from the ten studies, four had a clear impact on either policy or practice, and a further five had less clear impact, typically due to attribution issues, or are expected to be included in forthcoming guidance. We can also see a number of other types of impact, such as developing the credibility of research in a particular field, or building capacity to transfer policy into practice (NICE group, Cochrane review) as described in Chapter 3.

It is also important to note that this simplistic analysis of impact on policy and practice does not give an indication of the extent of implementation. Just because a treatment is recommended in a guideline, it does not necessarily mean that guidance has been taken up, as described above. Even if a treatment has been introduced into practice, we still need to consider how widely it is being used. We also need to consider how widely the treatment was used before the study took place – it may have been already quite widely used and hence not all implementation can be attributed to the work of the study. The counterfactual is also important: would the treatment have been introduced or used more widely even if this study were not conducted? Finally, attribution needs to be taken into account: to what extent was the treatment introduced because of this study, or are there other factors that were important, be that other pieces of research or wider environmental factors? Overall, this complexity of different considerations mean that it is very difficult, if not impossible, to accurately quantify the impact of the HTA Programme as a whole, or even this set of studies.

An important caveat here is that these case studies were selected for the study due to their potential for impact, so we might expect to see this high level of impact on policy, practice and other areas, and it is not possible to generalise across the full HTA portfolio based on a sample of this size. What we can do is look at the analysis for some of the studies that are identified in our economic analysis and are also described as case studies, to look at the extent to which their findings have been taken up and how far this

can be attributed to the HTA-funded research. This can give us some sense of whether the potential economic benefit calculated is likely to be observed in practice for these cases, though again this cannot be generalized.

**Table 3 Evidence of impact identified in case studies**

	Clear impact on policy	Clear impact on practice	Possible impact on policy (attribution issues)	Possible impact on practice (attribution issues)	Expected to be included on forthcoming guidance	Other type of impact
CESAR				√		
THA-SR			√			
ARTISTIC-2				√		
CRASH 2	√	√				
Acupuncture						
3MG					√	
EVAR	√	√				
NACHBID		√			√	Renewed interest in psychosocial treatment, established NICE project team
PACMAN				√		First RCT in UK critical care, new Cochrane review
DIGEM	√				√	

For example, the CESAR study, according to our economic analysis, has a potential net benefit of £440,527, based on 350 cases per year. The case study suggests that the number of beds has doubled to 190, and the number of ECMO centres increased from one to five. This suggests a significant increase, but it is important to note that this indicates some treatment was already in use before the study was conducted. It is also important to note the importance of attribution. The spread of H1N1 may have had more impact on the number of beds than this study. However, this would also have increased the number of cases benefitting from this treatment. In the case of THA-SR, by contrast, there has been a change in guidance, but we are not clear on the extent to which that has been taken up in practice, and in any case it is challenging to say whether this is attributable to this study in particular.

The work by Vickers et al. (2004) looking at acupuncture for headache had a potential net benefit of £121,213,761, based on 723,236 cases per year. According to the evidence identified through the case study, about 10% of GPs were already referring patients for acupuncture treatment for chronic headache when the study took place. We found no clear evidence on whether this increased after the study had been conducted, and it is not yet recommended in NICE guidance. Therefore, we have no clear evidence on the extent to which this potential benefit has been realised, but it is likely to be significantly less than 100%.

The ARTISTIC study had a potential net benefit of £2,914,937, based on 214,138 people per year screened. The evidence from the case study suggests that the HPV pre-screening was indicated as being cost effective by the trial and is currently being piloted in the UK with a view to potentially rolling it out across the UK. It seems that in this case the study was crucial in the development of this approach and is the main source referenced in the pilot material in relation to this pre-screening approach. It also seems that this is not an approach that had been considered prior to this study. Therefore, in this case, the study has the potential to achieve a large proportion of the potential net benefit suggested. However, it will depend on the success of the pilot stage, which introduces another factor which is not accounted for in this analysis, which is the time lag between the study and the realization of the potential benefit to the NHS. It should also be noted that as vaccination for HPV grows, the relevant population for screening will decrease, so the relevant population for this analysis is likely to decline over time.

Clearly, based on our analysis, the extent to which the potential net benefits from the study are realised varies significantly, from the acupuncture study where it is not clear whether any of the benefit is realised, to the ARTISTIC study, where it is possible that a large proportion of the net benefit will be realised. It is not possible to provide a generalization on this as it will vary from study to study. However, our analysis also shows that only around 12 per cent of the benefit which is possible from this sample of studies needs to be achieved as a result of HTA-funded work to cover the costs of the whole HTA programme. That is, even if we assume that only 12 per cent of the potential net benefit we have calculated is truly achieved and can be attributed to HTA, and that there is no additional benefit resulting from the other HTA studies not included in our sample of 10, we still find that the benefits calculated cover the cost of the investment in the programme.

Another key point illustrated by these case studies is that there are many factors outside the control of the studies which can impede implementation. These include lack of implementation skills, media and patient group pressure, local political considerations, and inertia on the part of some key stakeholders. This demonstrated why it is not appropriate to completely hold the programme and the researchers involved to account for the extent of implementation (Cullum et al, 2004; Drummond et al, 1997).

#### 4.4. Observations about potential enablers of impact

We did identify some factors which could be considered to help ensure the HTA Programme maximises the possibility of the findings being taken up and put into practice. These factors are listed below, but it should be noted that where they draw on case study findings, care should be taken in generalising these across the portfolio given the number of case studies conducted. Rather they should be considered as observations.

- *Consider the full range of costs of implementation.* Conducting economic analysis to meet NICE requirements means that some types of costs are not included in most HTA studies. Although studies cover NHS costs, these are the costs of the intervention in practice. Typically, some of the costs and challenges involved in introducing a new intervention are not considered in the economic analysis, though some authors will mention them in the wider discussion. For example, there may be training requirements that are costly and time consuming. These factors can be a barrier to uptake and although perhaps not appropriate for inclusion in the economic analysis included in the study, they could be included in the discussion, along with the wider implications for use in practice and any suggestions for how such barriers could be overcome.
- *Consider the importance of timing relative to the revision of relevant guidelines.* There are several cases where NICE guidelines haven't been updated since the study was completed and hence the work has not had an impact on the guidance provided. In some cases, guidance was published shortly before the HTA work was published. There may be an opportunity to improve this situation by communicating with relevant guideline committees and perhaps providing pre-publication findings for them to take into account where relevant.
- *Continue to support things other programmes are less willing to support.* The case studies illustrated some examples of support for things such as long-term follow up of cohorts, and meta-analyses of data across trials which could be valuable in terms of applicability and relevance to practice but may not always be funded by other sponsors (according to these case studies).
- *Continue to identify unproven but used practice as well as new interventions.* Despite an increasing focus in the NHS on becoming an evidence-based organisation, there are still practices being used without evidence of their effectiveness. This can be for a variety of reasons from historical accident to extrapolation of effectiveness from related conditions. Four of the case studies demonstrated that the HTA can play a useful role in showing where practice is being used which is not evidence based and that in some of these cases implementation could lead to cost savings for the NHS.
- *Continue to require systematic reviews before primary research is commissioned.* Ensuring that primary research is only conducted where there is a gap in the evidence and that this primary research is appropriately powered to draw the necessary conclusions, based on a review of previous evidence, will help ensure the findings of HTA funded studies are relevant to policy and practice. This approach also helps to ensure that HTA studies meet a policy or practice need which has not been addressed elsewhere, reducing the complexity around attribution when considering impact. However, this needs to be considered alongside timing, and possibly coordination with other funders, so that the time between the review and the trial does not result in duplication of effort.
- *Improve meta-data on studies.* The HTA has an ongoing project to develop meta-data across its clinical trials (NIHR HTA - 08/117/01). Gathering meta-data of this type across the HTA portfolio would support these types of analyses and allow for easier and more robust sampling. It would also enable the results of relevant HTA studies to be identified, classified

and used more readily. This could promote both better analysis of the HTA Programme, and better use of its study findings.

- *Ensure consistency of economic analyses.* The type and quality of economic analysis included in the HTA studies differs between studies, however, typically the economic analysis has become more standardised over time partially as a result of the updated guidance from NICE on the requirements for economic analysis. Several case studies showed the important of these economic analyses to the overall impact of the study, so ensuring their quality and consistency is important, and could also better enable this type of cross case analysis.

## Annex 1: Economic analysis

Table 4 Economic analysis, based on a value of £20,000 per QALY

Author	Incremental QALY gain	WTP Health Gain Unit	Incremental Cost	Prices (Year)	Incremental Cost (2012 Prices)	NMB per person Total	Total Cases in the UK	Total Net Benefit
Peek et al. 2010	3.66	£20,000	£48,533	2005	£59,415.70	£13,784	350	£4,824,506
Carroll et al. 2011	0.58	£20,000	£7,952	2012	£7,952.00	£3,648	14479	£52,818,108
Vickers et al. 2004	0.021	£20,000	£189	2003	£252.40	£168	723236	£121,213,761
Gilbert et al. 2004	0.07	£20,000	£61	2000	£92.85	£1,307	260000	£339,857,985
McCarthy et al. 2004	N/A b/c insignificant	£20,000	-£5	2000	-£8	£5	1322709	£6,613,547

RAND Europe

Cochrane et al. 2005	0.024	£20,000	£166	2002	£0.08	£480	1763613	£846,388,207
Lamb et al. 2010	0.099	£20,000	£178	2008	£196	£1,784	598000	£1,066,697,071
Pandor et al. 2013	0.1038	£20,000	£992	2012	£992	£1,084	504689	£547,082,762
Orlando et al. 2013	1.6239	£20,000	£22,528	2012	£22,528	£9,950	947	£9,420,660
Kitchener et al. 2009	N/A b/c insignificant	£20,000	-£12	2007	-£14	£14	214138	£2,914,937
							<b>TOTAL Net Benefit</b>	<b>£2,994,916,607</b>
							<b>TOTAL Cost</b>	<b>£367,000,000</b>

Table 5 Economic analysis, based on a value of £30,000 per QALY

Author	Incremental QALY gain	WTP Health Gain Unit	Incremental Cost	Prices (Year)	Incremental Cost (2012 Prices)	NMB per person Total	Total Cases in the UK	Total Net Benefit
Peek et al. 2010	3.66	£30,000	£48,533	2005	£59,415.70	£50,384	350	£17,634,506
Carroll et al. 2011	0.58	£30,000	£7,952	2012	£7,952.00	£9,448	14479	£136,794,266
Vickers et al. 2004	0.021	£30,000	£189	2003	£252.40	£378	723236	£273,093,314



*Returns on research funded under the NIHR Health Technology Assessment (HTA) Programme*

Gilbert et al. 2004	0.07	£30,000	£61	2000	£92.85	£2,007	260000	£521,857,985
McCarthy et al. 2004	N/A b/c insignificant	£30,000	-£5	2000	-£8	£5	1322709	£6,613,547
Cochrane et al. 2005	0.024	£30,000	£166	2002	£0.08	£720	1763613	£1,269,655,207
Lamb et al. 2010	0.099	£30,000	£178	2008	£196	£2,774	598000	£1,658,717,071
Pandor et al. 2013	0.1038	£30,000	£992	2012	£992	£2,122	504689	£1,070,949,835
Orlando et al. 2013	1.6239	£30,000	£22,528	2012	£22,528	£26,189	947	£24,795,745
Kitchener et al. 2009	N/A b/c insignificant	£30,000	-£12	2007	-£14	£14	214138	£2,914,937
							<b>TOTAL Net Benefit</b>	<b>£4,980,111,477</b>
							<b>TOTAL Cost</b>	<b>£367,000,000</b>



## Annex 2: Calculation of Total Cases in the UK

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**Table 6 Calculation of Total Cases in the UK**

Author	Total Cases	Calculation
Peek et al. 2010	350	According to Peek et al. (2010), "there may be as many as 350 adult patients with severe, but potentially reversible, respiratory failure in the UK each year." Therefore, we assumed that the total number of cases in the UK was 350. <b>Total Cases=350</b>
Carroll et al. 2011	14,479	According to Carroll et al. (2011), "the annual rate of hip fracture in women in the UK has been reported to be exponentially distributed and to be 20 per 10,000, 38 per 10,000, and 73 per 10,000 at 65, 70 and 75 years of age, respectively. Only 5% of fractures occur in men and women under the age of 60 years." And, according to the 2011 Census, the total number of women aged 65–69 years is 1,626,032, 70–74 years is 1,170,152 and 75–79 years is 928,768 (ONS, 2011). Therefore, we assumed that a conservative estimate of the total number of cases (about 95% of cases) in the UK was as follows: <b>Total Cases=(1,626,032*0.002)+(1,170,152*0.0038)+(928,768*0.0073)</b>
Vickers et al. 2004	723,236	According to Vickers et al. (2004), "the results suggested that 1.8–2.7% of the practice population would be potentially eligible for the study (aged 18–65 years, consulted for migraine or headache and/or receiving a prescription for migraine). And, according to the 201 Census, the total number of individuals aged 18–65 years in the UK is 40,179,776. Prevalence is 1.8–2.7% of adults (18–65 years) in GP practices (in HTA report). UK Population population 18–65 is 40179776 (ONS, 2011)). Therefore, we assumed that a conservative estimate of the total number of cases in the UK was as follows: <b>Total Cases=401,797,776*0.018</b>

RAND Europe

Gilbert et al. 2004	260,000	<p>According to a NICE Report on low back pain, 2.6 million people per year consult their GP about lower back pain (NICE, 2009) and according to Gilbert et al. (2004), "although most episodes of back pain are self-limiting, 10–20% of patients are referred to secondary care for a specialist opinion." Therefore, we assumed that a conservative estimated of the total number of cases in the UK was as follows:  <b>Total Cases=2,600,000*0.1</b></p>
McCarthy et al. 2004	1,802,168	<p>According to McCarthy et al. (2004), "it is estimated that, in the UK, 7.5% of people over the age of 55 years have some knee pain and disability associated with radiographic evidence of osteoarthritis, and that 2% have severe problem." According to the 2011 Census, there are 17,636,125 individuals over the age of 55 in the UK. Therefore, we assumed that a conservative estimate of the total number of cases in the UK was as follows:  <b>Total Cases=17,636,125*0.075</b></p>
Cochrane et al. 2005	1,763,613	<p>According to Cochrane et al. (2005), "from surveys conducted in UK populations, Peat and colleagues report that 10% of those aged over 55 have knee OA". According to the 2011 Census, there are 17,636,125 individuals over the age of 55 in the UK (ONS, 2011). Cochrane et al. (2005) also noted that, "in England and Wales between 1.3 and 1.75 million people were affected by OA." Therefore, we assumed that an appropriate estimate of the total number of cases was as follows:  <b>Total Cases=17,636,125*0.1</b></p>
Lamb et al. 2010	598,000	<p>According to a NICE Report report on low back pain, 2.6 million people per year consult their GP about lower back pain (NICE, 2009) and "estimates for the adult population burden of chronic back pain include; 11% for disabling back pain in the previous three months, 23% for low back pain lasting more than three months and, 18% for at least moderately troublesome pain in the previous month." Therefore, we assumed that an appropriate estimate of the total number of cases was as follows:  <b>Total Cases=2,600,000*0.23</b></p>
Pandor et al. 2013	568,724	<p>According to Pandor et al. (2013), "a UK population survey in 2009, drawing on an audit of GP registries, estimated total all–age prevalence of HF to be 0.9% for men and 0.7% for women." According to the 2011 Census, the total male population in the UK is 31,173,914 and the total female population is 32,017,667. Therefore, we assumed that an appropriate estimate of the total number of cases was as follows:  <b>Total Cases=(31,173,914 *0.009)+(32,017,667*0.007)</b></p>

Orlando et al. 2013	947	<p>According to Orlando et al. (2013), "some patients suitable for SAVR may receive TAVI; this could include both patients who would receive SAVR in the absence of TAVI and some patients who choose not to undergo surgery. Some patients unsuitable for SAVR would receive TAVI rather than medical managements. In the base-case analysis, this last group represents 90% of the patients receiving TAVI, a further 9% being those who would receive SAVR. Base case assumes that 90% of TAVI are conducted among those for whom SAVR is contraindicated. Given that there were 1052 TAVIs conducted in 2011, this analysis assumes that 90% of the 1052 TAVIs were for patients unsuitable for SAVR." And, according to Kovac et al. (2012), there were 1052 TAVIs conducted in the UK in 2011. Therefore, we assumed that an appropriate estimate of the total number of cases was as follows:  <b>Total Cases=1052*0.9</b></p>
Kitchener et al. 2009	214,138	<p>According to Kitchener et al. (2009), "in Round 1 there were 313 CIN3+ lesions, representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively" and "at the time the trial began in 2001, NHSCSP guidelines recommended that women aged 20 to 64 should participate in cervical cancer screening every 3–5 years. In 2003, national guidelines were changed so that those women under 25 were no longer invited to attend cervical screening." And, according to the 2011 Census, the female population aged 25 to 64 is 16,861,238. Therefore, we assumed that an appropriate estimate of the total number of cases was as follows:  <b>Total Cases=16,861,238*0.0127</b></p>

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## Annex 3: Full text of case studies

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This section provides the full text of all ten case studies conducted. A description of the methods used, and observations across the case study set is provided in Chapter 2. The case studies conducted are listed in the table below.

**Table 7 List of case studies conducted**

Volume and Issue in HTA journal	Title of study	Year of publication in HTA journal
14/35	CESAR: Randomised controlled trial and parallel economic evaluation of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure	2010
15/36	THA-SR: Hemiarthroplasty and total hip arthroplasty for treating primary intracapsular fracture of the hip: a systematic review and cost-effectiveness analysis	2011
13/51	ARTISTIC-2: A randomised trial of human papillomavirus (HPV) testing in primary cervical screening	2009
17/10	The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients	2013
8/48	Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis	2004
18/22	3MG: Intravenous or Nebulised Magnesium Sulphate Versus Standard Therapy for Severe Acute Asthma	2014
16/9	The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy	2012
13/21	NACHBID: Neuroleptics in the Treatment of Aggressive Challenging Behaviour for People with Intellectual Disabilities	2009
10/29	PACMAN: An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial	2006
13/15	DIGEM: Blood glucose self-monitoring in type 2 diabetes: a randomised controlled trial	2009

## The CESAR case study

### *Description of the Study*

The CESAR (Conventional ventilation or ECMO for Severe Adult Respiratory failure) RCT was a nationwide trial. It considered the hypothesis that extracorporeal membrane oxygenation (ECMO), when compared to conventional management (CM), improves survival without severe disability at six months for adults (18–65 years) with severe but potentially reversible respiratory failure. The primary outcome measure was death or severe disability at six months. CESAR was a UK-based multicentre trial, where the project team used an independent central randomisation service to randomly assign 180 adults in a 1:1 ratio that either received continued conventional management or referral to consideration for treatment by ECMO. Eligible patients were aged 18–65 years and had severe (Murray score  $>3.0$  or pH  $<7.20$ ) but potentially reversible respiratory failure. Exclusion criteria from the trial were: high pressure ( $>30$  cm H<sub>2</sub>O of peak inspiratory pressure) or high FiO<sub>2</sub> ( $>0.8$ ) ventilation for more than seven days, intracranial bleeding or any other contraindication to limited heparinisation. The trial was run on different participating clinical units, including the EMCO centre at Glenfield Hospital, Leicester, and more than 100 approved conventional treatment centres and referring hospitals in the UK.

The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme and the clinical treatment costs were funded by the NHS via the National Specialist Commissioning Advisory Group for England and Wales, and the Scottish Executive. The total HTA funding of the study was £1m and according to an interviewee from the project team, additional clinical costs of the study were £5million a year of the trial (Interview Data).

The findings of the CESAR trial were first published in the *Lancet* in 2009 and then in the National Institute for Health Research's Journal, *Health Technology Assessment*, in July, 2010. The HTA report included a full economic analysis of the cost-effectiveness of ECMO.

### *Context of the study*

The ECMO therapy was developed in the USA by Robert H. Bartlett, who took his inspiration for extracorporeal organ support from the heart and lung machine. The first successful treatment of an adult was in California in 1971 (University Hospitals of Leicester). In 1989, having been inspired of the merits of ECMO, the technology was introduced to the UK by Andrzej Sosnowski and Richard Firmin, based at Glenfield Hospital. At the time of the trial, mortality and morbidity of patients with acute respiratory distress syndrome in the adult population was high, with mortality rates for such patients between 34–58 per cent. Furthermore, surviving patients could have clinically significant physical disabilities. These could be both physical (respiratory and musculoskeletal) and neuropsychological (emotional and cognitive) disabilities. Such patients need inpatient rehabilitation and hospital readmissions, leading to high financial burden on carers and the healthcare systems. CM is characterised by intermittent positive pressure ventilation, which can cause very high airway pressures and oxygen concentrations, while the combination of barotrauma, volutrauma, biotrauma and toxic effects of oxygen exacerbates lung injury. According to the authors, the paradox behind CM is that the patients with the most severe lung injury require the



highest ventilator settings and are therefore most at risk of ventilator-induced lung injury. In comparison, ECMO uses cardiopulmonary bypass technology to support gas exchange in the intensive care unit instead, allowing ventilator settings to be reduced.

The research team states, that at the time of the trial, ECMO had only been proven in a RCT to increase survival in severe neonatal respiratory failure, but its use in adults had not been validated at that point in time. The authors were familiar with the existing literature of ECMO, as they were the leading members of the international ECMO community. The authors identified only two reported RCTs (Zapol et al., 1979; Morris et al. 1994), both for the US only. The other relevant evidence stemmed from observational studies which, as is generally known, suffer from potential biases.<sup>10</sup> After a period of applying for grants, the research team successfully got funding for the work in 1999 (Interview Data). In 2000, they started to recruit centres for patient enrolment that were suitable for the trial, where the type of centres included the ECMO centre at Glenfield Hospital, Leicester; conventional treatment centres (CTCs) and referring hospitals (RHs). Overall, 103 hospitals obtained the ethics committee approval to collaborate in the study, of which 92 were CTCs and 11 were RHs. Between 2001 and 2006, patients were randomly allocated into the trial's arms. As NICE appraisals should adopt the NHS perspective, but the ECMO technology is likely to have an economic impact further than only through healthcare requirements, at the time of the trial, the authors have chosen to include the NHS and the societal perspective.

### *Findings of the study*

Between July 2001 and August 2006 enquiries about 766 potentially eligible patients were made. Of those, 180 were randomised from 68 centres (90 in each trial arm). Of the 90 patients randomised to the ECMO arm, 68 received the treatment, while 90 entered the CM arm. Fewer patients in the ECMO arm died compared to the CM arm. Also the number of severe disabled patients after six months randomisation was smaller in the ECMO arm (36.7 per cent ECMO to 52.9 per cent CM). This equates into one extra survivor for every six patients treated. The average total cost to patients incurred by ECMO was £73,979 compared with £33,435 for those undergoing CM (including costs to the patient and their relatives, out of pocket and time costs). ECMO is therefore considered to be an expensive technology. Lifetime QALYs were calculated based on the assumption that quality of life of all surviving patients improved up to 24 months from randomisation and that after those 24 months, their health states mirrored that of other adults in the same age and gender group in the UK population. The economic evaluation of the trial revealed that the predicted cost per QALY of ECMO are £19,252, whereas the lifetime QALY gains of 10.75 for the ECMO group, compared to 7.31 for the CM. The ECMO technology showed a clear increase in survival, which was seen as the main outcome measure in the CESAR trial. Nevertheless, the findings of the economic analysis illustrated that ECMO is highly likely cost-efficient compared to CM, with an incremental cost of £48,533 and incremental lifetime QALY gain of 3.66. The probability that intervention was cost-effective at the £30,000 threshold is about 70 per cent.

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<sup>10</sup> A key source of bias, for example, is through the confounding of any results found with other factors resulting from selection biases.

### *Impact*

CESAR was the first contemporary RCT of ECMO referral for respiratory failure in adults. Note that the intervention in the CESAR trial was actually referral to an ECMO centre, not treatment with ECMO per se. In fact, only about 75 per cent of ECMO-referred patients actually received ECMO as treatment (Wallace et al. 2010). Nevertheless, the effects of the study were impressive: management of adults with severe respiratory failure at a centre with ECMO capability increased six-month survival without severe disability and referral to ECMO was cost-effective from the NHS perspective.

In the view of the CI, the main challenge for the study was to convince people that ECMO is a valid technology and therefore it needed huge effort to change the culture in the health service (Interview Data). Initially, ECMO did not receive a benevolent reception from healthcare practitioners and commissioners and the research team noted resistance to their findings. However, public perception changed in favour of ECMO after the outbreak of H1 N1 (swine flu). ECMO became a vital tool for battling swine flu, as ECMO is seen as 'the treatment of last resort' to patients most severely affected by the virus and whose inflamed and congested lungs have ceased to function under assault from the H1N1 virus (Laurance 2010). With the 2009 swine flu pandemic there were only 15 ECMO beds in the UK available and the technology made major headlines in the media when due to a shortage of ECMO machines in the UK a swine flu patient had to be flown to Sweden for treatment (Interview Data). After the initial surge of severe swine flu cases the ECMO capacity almost doubled to 190 beds in intensive care (Laurance 2010). Today, there are five adult ECMO centres in the UK: Glenfield Hospital, Leicester; Papworth Hospital, Cambridge; Wythenshawe Hospital, Manchester; Guy's & St Thomas' Hospital, London; Royal Brompton & Harefield Hospital; London. It is also worth noting that Glenfield Hospital became one of the world's most experienced hospitals in using ECMO, offering specialist training courses for national practitioners and people from Europe, the Middle East, Asia and Australia.

## THA-SR case study. Hemiarthroplasty and total hip arthroplasty for treating primary intracapsular fracture of the hip: a systematic review and cost-effectiveness analysis

### *Description of the study*

Hip fracture is a common problem in people aged 60 years and over. Due to increasingly ageing populations the absolute number of hip fractures is expected to rise (Cummings et al. 2002; Macaulay et al. 2006; Riggs and Melton 1995). Half of all hip fractures are displaced intracapsular fractures, which are unstable fractures in which the blood supply to the top of the femur may be impaired, affecting the rate of fracture healing (Keating et al. 2005; Parker et al. 2005; Singer et al. 1998). In these cases, the treatment options following hip fracture depend on the level of mobility prior to the fracture. For people who were mobile and capable of independent living prior to the fracture there are two treatment options: hemiarthroplasty (HA) and total hip arthroplasty (THA) (Bhandari et al. 2005; Crossman 2002; Parker et al. 2000). In HA just the ball joint at the top of the femur is replaced, whereas in THA the part on the hip which the femur intersects is also replaced. As such the HA operation is a little simpler and quicker, and it is the standard intervention. The aim of this study was to conduct a systematic review of the existing data on this topic in order to assess the clinical and cost effectiveness of THA compared with HA in patients with displaced intracapsular fracture who are cognitively intact with high pre-fracture mobility or function.

The study was conducted between September 2010 and October 2011, led by Dr Christopher Carroll at the University of Sheffield. The results of the study were published as a *HTA* report in October 2011 (Carroll et al. 2011).

### *Context*

This work was directly commissioned by the HTA as part of the contract that they have with the School of Health and Related Research at the University of Sheffield. Prior to this study, in the UK the vast majority of mobile patients with a displaced intracapsular hip fracture are treated by HA rather than by THA (Leighton et al. 2007). As reported in the study, a survey of 223 UK hospitals in 2000 reported that, for active patients, HA was undertaken at 73 per cent of hospitals, THA at 16 per cent and internal fixation at 37 per cent (the proportions exceed 100 per cent as some hospitals reported using more than one method of treatment) (Crossman 2002). Prior to this work, there was no consensus regarding the optimal treatment for individuals who are cognitively intact and with high pre-fracture mobility or function.

Initially, the project team were asked to undertake a scoping phase to establish what evidence was available which looked at results after treatment for three years or longer. They found that there were only three RCTs meeting these criteria, but there were some other studies with shorter term outcomes measured that could contribute to their analysis. The team were commissioned to carry out the full review and these results were published in October 2011.

Prior to this study, a Cochrane review had been done on the topic (Parker et al. 2010). In addition, a *BMJ* review on this topic was published in 2010 while this work was ongoing (Hopley et al. 2010). This review

used less stringent exclusion criteria but the findings were broadly similar to those of this study. In both cases, these reviews focused on clinical effectiveness only and did not include a cost effectiveness analysis.

### *Findings of the study*

The study was a systematic review of randomised controlled trials (RCTs), looking at the effectiveness of THA compared with HA using outcome measures covering dislocations, revisions, pain and function, and quality of life. The study also included meta-analysis, independent subgroup analyses and exploratory cost-effectiveness modelling. They found that all of the existing trials, along with their meta-analysis had broadly similar findings. THA was associated with an increased likelihood of dislocation than HA which then had to be managed. HA had a much higher likelihood in comparison to THA of a revision being necessary – that is, additional surgery being needed (typically to conduct a THA). However, quality of life was almost always found to be better under THA than HA, using a quality of life measure that took function and mobility into account, as well as psychological factors. Therefore, although both treatments had potential medical issues, THA was likely preferable due to the quality of life benefits conferred.

Cost effectiveness analysis conducted as part of the study also concluded that THA is likely to be preferable to HA. The analysis suggested that THA is likely associated with increased costs in the first two years, but with lower costs over the long term due to lower revision rates. However, it should be noted that these longer term costs were not modelled. Additionally, it should be noted that the capacity and experience of surgeons to conduct THA were not explored and that such training needs would need to be taken into account at the local level for this to become recommended as standard of care. THA is a more complex procedure and as such is likely to need a more experienced clinician to carry it out. Typically THA is only performed by senior clinicians whereas a wider group of surgeons are likely to be able to carry out HA. The potential training costs, or impact on waiting times for treatment, are not accounted for in the analysis and this could be an impediment to implementation of these findings within the NHS. The study suggests that further work could be conducted to look at the impact of surgeon experience when performing the two procedures on outcomes.

### *Impact*

Guidance on treatment of hip fracture was published in August 2011 before the final results of this work was published (although the work was finalised and sent to the HTA in May) (NICE 2011). That guidance aligns with the findings of this study, recommending THA as the first choice of treatment for mobile, independent adults with hip fracture.

## Cervical cancer screening (ARTISTIC) case study

### *Description of the study*

The ARTISTIC study was a randomised trial of human papillomavirus testing in primary cervical screening. The intent of the study was to determine whether HPV testing coupled with the standard micro-cytology analysis would be more effective in and/or sensitive to detecting underlying disease. As HPV has become accepted as the major disease factor in cervical cancer, the hypothesis was that there would be an increased detection of cervical cancer if tested for both HPV and cervical cytology (Kitchener 2014). Because the study had to piggyback on standard procedure of cytology screening for women, any HPV testing had to be done together with the cytology samples. As a result, the study was divided into three arms, with one arm having its HPV test concealed from participants, and the other two with it open and reported. Furthermore, the structure of the study allowed the study to determine the effectiveness and cost structures of three scenarios: cytology and HPV, cytology alone, and HPV alone (Kitchener et al. 2009).

The test was carried out with a liquid based HPV and cytology sample (unique compared to others). The study was also divided into three rounds, though only two were completed before the study results had to be reported. The first round was the entry round where the first 'cytologically' adequate sample after randomisation was taken. The second round was a follow up round in which the first cytologically adequate sample was taken after 30 and 48 months (Kitchener et al. 2009). The first two rounds were from 2001-2008; a third round followed from the last 12-18 months of the study and went to 2011.

In total, from Round 1 24,510 women aged 20-64 years were enrolled. Round 1 and Round 2 of the study cost £1.8m and the follow-on Round 3 cost £400,000.

The study was reported in the following articles:

- Kitchener et al. 2009. *Health Technology Assessment* 13(51).
- Kitchener, H.C., Almonte, M., Wheeler, P., Desai, M., Gilham, C., Baily, A., Sargent, A., Peto, J. 2006. 'HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial.' *British Journal of Cancer* 95: 56-61.
- Kitchener, H., Almonte, M., Thomson, C., Wheeler, P., Sargent, A., Stoykova, B., Gilham, C., Baysson, H., Roberts, C., Dowie, R., Desai, M., Mather, J., Bailey, A., Turner, A., Peto, J., Moss, S. 2009. 'HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial.' *The Lancet Oncology* 10(7): 672-682.
- Kitchener, H.C., Gilham, C., Sargent, A., Bailey, A., Albrow, R., Roberts, C., Desai, M., Mather, J., Turner, A., Moss, S., Peto, J. 2011. 'A comparison of HPV DNA testing and liquid based cytology over three rounds of primary cervical screening: Extended follow up in the ARTISTIC trial.' *European Journal of Cancer* 47(6): 864-71.
- Sargent, A., Bailey, A., Almonte, M., Turner, A., Thomson, C., Peto, J., Desai, M., Mather, J., Moss, S., Roberts, C., Kitchener, H.C., ARTISTIC Study Group. 2008. 'Prevalence of

type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial.' *British Journal of Cancer* 98: 1704–1709.

- Sargent, A., Bailey, A., Turner, A., Almonte, M., Gilham, C., Baysson, H., Peto, J., Roberts, C., Thomson, C., Desai, M., Mather, J., Kitchener, H. 2009. 'Optimal Threshold for a Positive Hybrid Capture 2 Test for Detection of Human Papillomavirus: Data from the ARTISTIC Trial.' *Journal of Clinical Microbiology* 48(2): 554–558.

The work was also part of a four study report in the following:

- Ronco et al. 2010. 'Efficacy of human papillomavirus testing for the detection of invasive cervical cancers and cervical intraepithelial neoplasia: a randomised controlled trial' *The Lancet Oncology* 11(3): 249–257.

## Context

Before the study was carried out, the standard of care up to 2012 to 2014 was to use cytology alone. This mostly involved taking a smear test from women of cervical cells and analysing them for lesions which may indicate pre-cancerous or cancerous cells. However, over the last thirty years, the role of HPV in the cause of cancer has been established with the implication that such cancer can be prevented through a vaccine, and HPV detection can be used as a diagnostic (Kitchener et al, 2009; Kitchener 2014). There were non-randomised studies that HPV screening could be useful, and the development of commercial tests, but no large scale study was done to rigorously test the screening systems.

According to the principal investigator, the NIHR (through the HTA Programme) realised that they would have to conduct a large randomised trial in order to explore whether (and what) implications for changes in practice these discoveries would hold, and whether HPV screening would be implemented in standard practices. Three other countries also held publicly-funded trials in this regard including Italy, the Netherlands and Sweden (Kitchener 2014).

Furthermore, adding to the context of the study and its timeliness, HPV vaccinations were being implemented as part of a national programme in 2008. If the HPV vaccinations result in a far larger proportion of the population to be HPV negative, then it makes sense to switch screening to the HPV virus.

The idea of HPV virus testing is also based on the fact that HPV testing is either a positive or negative and therefore more objective if the sample and test are carried out properly, whereas cytology screening can be more dependent on the laboratory analyst.

## Findings of the study

The study failed to determine by the second round of funding that a combined HPV screen and cytology test would be more sensitive to disease detection. What was found, however, was that HPV alone as a triage or as an initial test triaged by cytology would be significantly cheaper than beginning with cytology-based screening. Furthermore, with the liquid based sampling, the same HPV sample used for the initial triage could be used for later cytology analysis, thereby eliminating the need for the woman involved to return to the hospital/clinic for a second sample.

The problems with HPV testing alone is that there is a relatively high prevalence of HPV amongst women younger than 30 years of age, however the level of true viral persistence may be lower depending on the type of HPV (which the study states need to be better categorised to determine). However, a different problem exists with cytology studies in that some women who test negative with a cytology test still develop cervical cancer, whereas this does not happen to a significant degree amongst women who receive a negative result on a HPV test (Kitchener 2014).

Given the different scenarios of screening carried out by the study, the authors concluded that the cost for just a cytology screen and possible colposcopy check would be £51.56 (per patient) versus £65.04 for including the HPV screen for Round 1. For Round 2 the cost would be £72.18 versus £91.54. The authors then estimated that for 26,800 women in the Manchester area in 2006–7 the cost over three years would be £1,390,000 versus £1,743,000 including the added HPV screening. Because of the relatively minor improvement (non-significant in the ARTISTIC trial) found when using both HPV screening and cytology together, the increased cost could not be justified. However, the trial also noted the effectiveness of using HPV screening as a triage, and the implications of possible cost savings with the caveat that a possible increase in colposcopy visits may occur for follow-up cases. As a result, the authors predict that the HPV screening would have a positive economic impact, especially in the longer-term in conjunction with the HPV vaccine (Kitchener et al, 2009).

A secondary or tangential, but still important finding was that the screening threshold or cut-off for HPV screening issued by the original manufacturer of the HPV test was too sensitive resulting in many false positives (Kitchener 2014). As a result, with changes to the cut-off, the study was able to come up with a test that resulted in less false positives but was still sensitive enough to offer effective screening. A test that is well balanced in terms of its cut-off can also help to avoid too many colposcopy referrals that may not be necessary.

### *Impact*

No plans were made to change cervical cancer screening procedures prior to the release of the results of the ARTISTIC study. With the close of the initial study and its inclusion into a larger pooled study, there has been a pilot study launched to implement the recommended changes of using HPV screening as a triage, followed by the cytology methods. Coupled with the HPV vaccination programme, it is predicted that the size of the screening programme will shrink as more women become immune. As it stands, therefore, the implications of the study (the changes in screening coupled with the HPV vaccine) will affect approximately 25 per cent of the population (women from their early twenties to mid-sixties) (Kitchener 2014).

Furthermore, the study also led to a changing of the screening period being increased to five years between screenings rather than only three. Savings will be garnered from this.

However, one challenge noted by the authors was that it would be challenging to explain the importance of follow-up to women who test positive for HPV but negative in their cytology screening as they may still be at risk. The more complicated message to the patient group may make complete follow up more difficult.

## Clinical Randomisation of an Anti-fibrinolytic in Significant Haemorrhage (CRASH-2) on trauma patients. Case study

### *Description of the study*

The CRASH-2 study was begun in May 2005, recruiting 20,211 patients in 274 hospitals across 40 countries, with the results reported in 2010. CRASH-2 was a clinical randomisation trial to test the antifibrinolytic tranexamic acid (TXA) to control or lower bleeding and therefore risk of death in trauma victims versus a placebo (Roberts et al. 2013).

The study is introduced with the statistic that every year three million people die of trauma worldwide (serious injury), and a third of people who die of trauma die of blood loss. TXA has already been in use to reduce bleeding in patients undergoing surgery by encouraging clotting and preventing blood clots from breaking down. CRASH-2 was therefore an attempt to see whether the same drug – a low cost generic drug – could be used to treat trauma victims shortly after their injury and reduce their chance of dying (Roberts 2014). It would also test to see whether there were any adverse effects due to clotting.

The main findings of the study were reported in the following articles:

- *CRASH-2 trial collaborators.* 2011. 'The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial'. *Lancet* 377(9771):1096–101.
- Guerriero, C., Cairns, J., Perel, P., Shakur, H., Roberts, I. CRASH 2 trial collaborators. 2011. 'Cost-Effectiveness Analysis of Administering Tranexamic Acid to Bleeding Trauma Patients Using Evidence from the CRASH-2 Trial'. *PLoS ONE* 6(5): e18987.
- Ker, K., Kiriya, J., Perel, P., Edwards, P., Shakur, H., Roberts, I. 2012. 'Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial.' *BMC Emergency Medicine* 12(3).
- Shakur, H., Roberts, I., Piot, P., Horton, R., Krug, E., Mersch, J. 2012. 'A promise to save 100 000 trauma patients.' *Lancet* 380(9859): 2062–2063.
- Roberts, I., Perel, P., Prieto-Merino, D., Shakur, H., Coats, T., Hunt, B., Lecky, F., Brohi, K., Willett, K. 2012. 'Effect of tranexamic acid on mortality in patients with traumatic bleeding: prespecified analysis of data from randomised controlled trial.' *BMJ* 345: e5839.
- Roberts, I., Shakur, H., Coats, T., Hunt, B., Balogun, E., Barnetson, L., Cook, L., Kawahara, T., Perel, P., Prieto-Merino, D., Ramos, M., Cairns, J., Guerriero, C. 2013. 'The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients'. *Health Technology Assessment* 17(10).

And in a systematic review:

- Cap, A.P., Baer, D.G., Orman, J.A., Aden, J., Ryan, K., Blackbourne, L.H. 2011.. 'Tranexamic Acid for Trauma Patients: A Critical Review of the Literature.' *Journal of Trauma-Injury Infection and Critical Care* 71(1 Suppl): S9-14.



## Context

Before the study, there was no plan on using TXA during trauma treatment. The impetus for the study came from a systematic study on TXA as used in surgery. The PI, as a member of the Cochrane Injury Group, saw the study and put forward the research question of whether TXA could therefore be effective in the event of trauma given the number of fatalities from trauma-induced blood loss. Different reviews are highlighted in the reference list from the Cochrane review, demonstrating the link between them and the subsequent research question (Roberts 2014).

As mentioned above, the study was framed globally in terms of the number of people dying from severe injury and bleeding. In terms of the UK, the study is further justified by the tendency of trauma victims to be younger adults who would otherwise be healthy. As a result, lowering the death rate amongst this population would contribute to helping the most economically productive members of society in terms of their phase of life. For less developed countries, the background of the study found that more people are at risk of death by trauma and that the economic impacts would be larger as many times the injury would occur to the main earner for household and families can quickly become destitute as a result.

## Findings of the study

The findings of the study were significant; it found that overall TXA reduced the risk of bleeding to death by 30 per cent if administered within the first hour of injury, and by 20 per cent if administered within the first three hours. After three hours, the effectiveness of the drug was not significant. Overall, it found that out of every 1,000 people who received TXA versus those who received a placebo, there was a reduction in death from bleeding by 15 per cent over a four-week period from the injury. The main challenge would therefore be to ensure mechanisms for individuals to receive treatment within the first three hours of their injury; while in advanced urban centres this may be easier, in other regions this may be more challenging (Roberts 2014; Roberts et al. 2013).

## Impact

The impact of the study has been significant, occurring in multiple stages and notable in practice in the UK. While the publication of the results occurred in the *Lancet* (2010), according to the PI the study's results were shared with the Surgeon General of the British Armed Forces informally before the end of the study resulting in some ad-hoc use of TXA for trauma treatment and in 2009 as part of a transfusion protocol. Following the *Lancet* publication, TXA began to be used systematically in trauma treatment in 2010. Following UK military use of TXA in its trauma treatment, the US military began to change its practice after a comparative study between the two forces and noting the increased survival rates among UK treated soldiers.

Furthermore, changes in trauma treatment in UK hospitals followed but more slowly as hospital protocols took longer to change. It is acceptable because of its cost-effectiveness and ease of application. Now, the UK trauma network TARN is implementing TXA use and 75 per cent of trauma victims in the UK are receiving it. According to the PI, NICE issued guidance based on the results of the study on how TXA could be used for trauma. Globally, the World Health Organization listed TXA as an essential medicine

RAND Europe

based on the CRASH-2 results (Roberts 2014). CRASH-2 has also led to further research interest and tests on other injuries such as brain injuries.

## Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis

### *Description of the study*

The objective of the study was to determine the effects of using acupuncture, compared with a control intervention offering usual care, on headache in primary care patients with chronic headache disorders. A subsequent objective was to determine the effects of treatment with acupuncture on other outcomes, such as medication use, quality of life, and days off sick as compared to no acupuncture. The study was conducted as an RCT in general practices in England and Wales including 401 patients with chronic headache disorder, predominantly migraine. In the trial, patients were randomised to the treatment group in which they receive up to 12 acupuncture treatments over a time period of 3 months or to the control group receiving the standard of care intervention (mainly medication, pharmacological treatments). The primary outcome measures included headache score, assessment of Short Form 36 (SF-36) health status and use of medication at 3 months and at 12 months, and use of resources at 3 months. The trial also included an economic evaluation to assess the incremental costs per QALY gained of acupuncture compared to no acupuncture.

The study reports that the headache score at 12 months was lower in the acupuncture group (mean 16.2 SD, corresponding to a 34 per cent reduction) than in the control group (22.3 SD, corresponding to a 16 per cent reduction). Patients in the acupuncture group experienced 22 fewer days of headache per year (8 in treatment compared to 38 in control). Compared to the control group, patients in the treatment group further used 15 per cent less medication, made 25 per cent fewer visits to GP and took 15 per cent fewer days off sick. In terms of QALYs, the mean health gain from acupuncture during the trial was 0.021 QALY, leading to £9,180 per QALY gained.

The trial was funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme and the clinical treatment costs were funded by the NHS via the National Specialist Commissioning Advisory Group for England and Wales.

The findings of the trial were first published in the *BMJ* in 2004 and then in the NIHR's journal, *Health Technology Assessment*, in November, 2004. The *HTA* report included a full economic analysis of the cost-effectiveness.

### *Context of the study*

Migraine and tension-type headache give rise to significant health, economic and social costs. Despite positive effects of medication intake, many patients affected continue to experience distress, which leads health professionals to recommend non-pharmacological approaches to the care of headaches. One popular approach therefore is acupuncture. At the time of the study, each week approximately 10 per cent of GPs in England either referred patients to acupuncture or practise it themselves. It is worth noting that chronic headache disorder is one of the most commonly treated conditions with acupuncture. At the time of the study, a Cochrane Collaboration review of 26 RCTs of acupuncture for headache concluded that existing evidence supports the value of acupuncture, but the quality and amount of evidence were not

fully convincing. The report stated that there was an urgent need for well-planned large-scale studies to assess the effectiveness of acupuncture under 'real-life conditions'. The study tried to address and bridge this existing gap in the acupuncture literature.

One major design concern of the study was to conclude what is the correct control group treatment. Rather than using a placebo comparison, the study team decided to compare acupuncture with a 'no treatment' control. The decision was made keeping in mind the intention was to reflect 'real-world decisions', as made by GPs when managing the care of headache patients and those made by patients who seek care. For instance, the decision made in a clinical practice is not that between referring to acupuncture or by referring to placebo, but between referring or not referring to acupuncture.

### *Findings of the study*

Recruitment for the trial took place between November 1999 and January 2001. Acupuncture patients received a median of nine treatments with a median of one treatment per week. The drop-out rate did not cause bias according to the authors as patients who dropped out were similar to completers in terms of gender, diagnosis and chronicity. In the primary analysis, mean headache scores were significantly lower in the acupuncture group (scores fell by 34 per cent in the treatment group, compared to 16 per cent in the control group). The difference in days with headache was 1.8 days per four weeks or equivalent to 22 fewer days of headache per year. Furthermore, medication scores at follow-up were lower in the acupuncture group, although not statistically significant. With regards to resource costs, the study showed that patients in the acupuncture group made fewer visits to GPs and complementary practitioners than those not receiving acupuncture and took fewer days off sick.

The economic evaluation of the study shows a mean health gain of acupuncture of 0.021 QALYs, which is according to the authors equivalent to eight quality-adjusted days. Mean incremental cost of the acupuncture intervention to the NHS was £205 per patient, excluding the impact on prescription drugs, which leads overall to an additional cost of £9,180 per QALY gained. The sensitivity analysis showed that at a ceiling of £30,000 per QALY, the intervention is cost-effective at 92 per cent.

### *Impact*

The results of the study suggest that acupuncture complemented by standard care can result in persisting and relevant benefits for primary care patients with chronic headache disorders. The study also found positive effects on quality of life, decreases in medication and GP visits. Compared to existing literature at the time of the study, the strengths of the study include a large sample size, concealed randomisation and careful follow-up. Therefore, the study was congruent with much of the prior literature on acupuncture for headache.

The recruitment for the trial revealed considerable headache morbidity in the UK population. About half of the patients were experiencing moderate to severe headaches on at least one out of every four days. One-quarter were experiencing moderate or severe headaches for 12 or more days per calendar month. Due to this, the study team concluded that at the time of the study, management of patients with headaches in primary care was not always efficient. In this case referral to acupuncture for patients with poorly managed chronic headache disorders appears to be worthy for consideration.

## 3Mg case study. Intravenous or nebulised magnesium sulphate versus standard therapy for severe acute asthma

### *Description of the study*

The 3Mg trial evaluated the effectiveness of three different interventions for the treatment of severe acute asthma, alongside standard treatment. The interventions were intravenous magnesium sulphate, nebulised magnesium sulphate and a placebo (Goodacre et al. 2014). At the time of the trial, standard treatment for severe acute asthma included the use of oxygen, nebulised salbutamol, nebulised ipratropium bromide and oral prednisolone, with additional salbutamol administered if necessary. The British Thoracic Society defines patients with severe acute or life threatening asthma as those that fail to respond to therapy. The definition encompasses those who demonstrate: deteriorating peak expiratory flow (PEF); persisting or worsening hypoxia; hypercapnea; arterial blood gas analysis showing fall in pH or rising H<sup>+</sup> concentration; exhaustion or feeble respiration; drowsiness; confusion; altered conscious state; or respirator arrest (BTS 2012). The total cost of the study was £1,727,163 (NIHR HTA - 06/01/02). The findings of the 3Mg trial were first published in the *Lancet* in May, 2013 and then in the NIHR's *HTA* journal in April, 2014 (Goodacre et al. 2013; 2014).

### *Context*

At the time that the 3Mg trial was undertaken, there was some evidence that magnesium sulphate could improve pulmonary function (BTS 2012). However, at the time of the trial, the British Thoracic Society guidelines on the use of magnesium sulphate were not clear. The guidelines indicated the safe level of magnesium sulphate to be administered to patients with severe asthma that have not responded well to inhaled bronchodilator therapy or to patients that have life threatening or near fatal asthma. However, the guidelines also note that, 'more studies are needed to determine the optimal route, frequency and dose of magnesium sulphate therapy.'(p64). Prior to conducting the 3Mg trial, Mohammed and Goodacre (2007) conducted a systematic review and meta-analysis of the effectiveness of both forms of magnesium sulphate. They found that there was some weak evidence that magnesium sulphate could improve respiratory function and reduce hospital admissions, although the effect on hospital admissions was not statistically significant. The authors concluded that intravenous magnesium sulphate appears to be effective in children but that further trials are needed of both forms of delivery of magnesium sulphate in adults and of nebulised magnesium sulphate in children. Nevertheless, according to a key informant interview, prior to the 3Mg trial, intravenous magnesium sulphate was widely used in the UK while nebulised magnesium sulphate was rarely used (Interview Data).

According to a key informant interview, at the time of conducting the 3Mg trial, the study investigators were not aware of any ongoing work on the use of intravenous or nebulised magnesium sulphate for the treatment of severe acute asthma in adults (Interview Data). Although, as the trial results were being published, a small study on the same area was also published in the *Iranian Journal of Allergy, Asthma and Immunology*. However, the HTA did fund a parallel trial looking at the effectiveness of magnesium sulphate in children with acute severe asthma, as results from a systematic review indicated that there was

quite good evidence of the effectiveness of intravenous magnesium sulphate for the treatment of acute severe asthma in children but almost no evidence for nebulised magnesium sulphate (Powell et al. 2013).

The main objectives of the 3Mg trial were to clarify whether intravenous magnesium sulphate or nebulised magnesium sulphate are effective treatments for adults with acute severe asthma (Goodacre et al. 2014). At the time of the trial, not only was there little evidence indicating that either treatment could improve clinical outcomes, but there were also no trials comparing the effectiveness of intravenous magnesium sulphate and nebulised magnesium sulphate. According to the 3Mg trial protocol, there were four main reasons for conducting a large clinical trial to compare the effectiveness of intravenous magnesium sulphate and nebulised magnesium sulphate relative to placebo. First, the studies included in the meta-analyses of intravenous and nebulised magnesium sulphate were relatively small. Second, publication bias may have resulted in an over-estimate of the effectiveness of magnesium sulphate. Third, the study by Rowe et al. that showed a clinically significant effect of magnesium sulphate used a post-hoc subgroup analysis. Fourth, a large trial would enable the comparison of the two forms of magnesium sulphate relative to placebo (Goodacre et al. 2011).

### *Findings of the study*

The results of the 3Mg trial were effectively negative (Goodacre et al. 2014). The authors conclusively found that there was no evidence of the effectiveness of nebulised magnesium sulphate. Moreover, there was even a slightly worse outcome for patients treated with nebulised magnesium sulphate, such that nebulised magnesium sulphate can be ruled out as a potential treatment for acute severe asthma. The results for intravenous magnesium sulphate were less clear. The authors found that there was a very small degree of improvement in breathlessness for patients treated with intravenous magnesium sulphate and a non-significant downward trend in hospital admission but no effect on respiratory function. The authors concluded that the findings of the 3Mg trial suggest that there is no role for nebulised magnesium sulphate in the treatment of severe acute asthma in adults and, at best, a limited for the use of intravenous magnesium sulphate in this patient group.

The findings of the economic analysis showed that placebo was the most cost-effective treatment. This result was primarily driven by the fact that the estimates of effectiveness showed no evidence of the effectiveness of nebulised magnesium sulphate and little benefit of intravenous sulphate. Although the cost of magnesium sulphate was low, variations in length of stay and admissions rates meant that overall, there was no evidence that either nebulised magnesium sulphate or intravenous magnesium sulphate were more cost-effective than placebo.

### *Impact*

Our information on the likely impact of this study are based on a key informant interview with a member of the study team. According to that interview, the findings of the 3Mg trial will likely have an impact on the guidelines for the treatment of patients with severe acute asthma (Interview Data). The most recent British Thoracic Society guidelines, from 2012, mentioned that they were awaiting the results of a trial comparing the effectiveness of intravenous and nebulized magnesium sulphate. It is therefore likely that the British Thoracic Society will consider the results of the trial in their next guidelines (Interview Data).

It is unclear whether the findings of the 3Mg trial have had an impact on clinical practice as the clinical results of the trial were published in May, 2013 (Goodacre et al. 2013) and the full HTA report was published in the National Institute for Health Care Research's journal, *Health Technology Assessment*, in April 2014 (Goodacre et al. 2014).

The interviewee suggested that the main barrier to the implementation of the 3Mg study's findings would likely be overcoming clinicians' a priori beliefs (Interview Data). They also suggested that at the time that Mohammed and Goodacre (2007) were conducting the systematic review and meta-analysis of intravenous and nebulised magnesium sulphate, there was a very strong belief among clinicians that intravenous magnesium sulphate was effective while nebulised magnesium sulphate was not. This was despite the fact that at the time there was similarly weak evidence of effectiveness for both treatments. This belief in the effectiveness of magnesium sulphate may stem from the fact that patients with asthma respond to concurrent treatments and also tend to respond spontaneously, which may create a very strong belief in the effectiveness of magnesium sulphate. The interviewee concluded that randomised trials can struggle to overcome clinicians' a priori beliefs even though the evidence from randomised clinical trials is much more robust than clinicians' anecdotal experience (Interview Data).

Based on the interview discussion, if the British Thoracic Society revises its guidelines as a consequence of the results of the 3Mg trial then the changes in the guidelines would then likely have a positive impact on patients with severe acute asthma presenting at emergency departments (Interview Data). For example, if clinicians' choose not to persist with medical treatments like intravenous magnesium sulphate but rather move on to other treatments that are more likely to be effective, such as supporting their ventilation, then this could have a positive impact on patients.

The interviewee also felt that in the long-term, it is not likely that the 3Mg trial will have a major impact (Interview Data). The main impact of the study findings will be to make the role of intravenous magnesium sulphate in the treatment of patients with severe acute asthma more clear. According to the same interviewee, the research team does not anticipate that intravenous magnesium sulphate will be removed from guidance completely. Rather, holds the interviewee, the emphasis from the guidance will be that clinicians should not expect an effect from magnesium sulphate and that patients who are not responding to initial treatments with acute asthma should have involvement in intensive care rather than more treatment with intravenous magnesium sulphate. Lastly, it is likely that the study will have an impact on future research in this area as the research team concluded that further research into magnesium sulphate it not warranted.

## The UK EndoVascular Aneurysm Repair (EVAR) trials: randomised trials of EVAR versus standard therapy

### *Description of the study*

Abdominal aortic aneurysm (AAA) is a condition in which the aorta – the main artery, which leaves the heart and travels down towards the legs – starts to bulge and expand at a section just below the diaphragm, level with the navel. In this region, the aorta normally measures about 1.5–2.5 cm in diameter but, with this condition, can grow much larger and in extreme cases can rupture requiring an emergency operation and often resulting in death (approximately 80 per cent mortality. Ingoldby et al. 1986). The prevalence of AAA is around 5 per cent in men over the age of 65 years (Collin et al. 1988) and tends to increase with age (Scott et al. 2001), but is far less common in women (Cornuz et al. 2004; Lerderle et al. 1997 & 2001). There is no proven medical therapy to cure or slow the growth of the aneurysm and surgical correction remains the only course of treatment (Guessous et al. 2008). Previous work has shown that surgical intervention is needed when the aorta exceeds 5.5cm in diameter, above which it is liable to rupture (UK SAT 1998).

Around 1991, a new technique became available for the correction of AAA: endovascular repair (EVAR). Prior to that, the standard treatment was open surgical repair which had been used since the late 1950s. EVAR is less invasive than open repair and can be performed under a local anaesthetic. This results in a shorter recovery time and a better chance of surviving within the first 30 days after the procedure. However, it is more likely for there to be problems following the operation that may require further small procedures to correct them. EVAR can also be used with patients that are not in good enough health to undergo surgery under general anaesthetic as required for open repair, since the surgery is more minor.

The aim of the study was to compare the efficacy of endovascular aneurysm repair (EVAR) with standard alternative management in patients with large abdominal aortic aneurysm (AAA) in two groups:

EVAR 1: comparing EVAR with open repair in patients deemed fit to undergo open repair

EVAR 2: comparing EVAR with medical management amongst patients fit to undergo EVAR but not open repair.

The study was undertaken between July 2005 and March 2012, and has also been funded recently to continue to follow the cohort until 2014 – 15 years post-treatment. The study cost £901,457.65 and was led by Professor Roger Greenhalgh at Imperial College London. The trial included nearly 40 UK centres at which staff was trained to undertake the new treatment. The protocol stated that a surgeon and a radiologist would work together to conduct the procedure, and the work was supported by the vascular society, the surgical society, and the society of radiologists. The findings were published as a HTA report in 2012 (Brown et al. 2012) and additionally through the following publications:

- Brown, L. C., Greenhalgh, R.M., Thompson, S.G., Powell, J.T. 2010. 'Does EVAR alter the rate of cardiovascular events in patients with abdominal aortic aneurism considered unfit for open repair? Results from the randomised EVAR trial 2.' *European Journal of Vascular and Endovascular Surgery* 39(2): 396–402.



- Greenhalgh, R., Powell, J. 2008. 'Endovascular repair of abdominal aortic aneurysm.' *New England Journal of Medicine* 358: 494–501.
- The United Kingdom EVAR Trial Investigators. 2010. 'Endovascular repair of aortic aneurysm in patients physically ineligible for open repair.' *New England Journal of Medicine* 362:1872–1880.
- The United Kingdom EVAR Trial Investigators. 2010. 'Endovascular versus open repair of abdominal aortic aneurysm.' *New England Journal of Medicine* 362: 1863–1871.
- Epstein, D., Sculpher, M., Manca, A., Michaels, J., Thompson, S., Brown, L., Powell, J., Buxton, M., Greenhalgh, R. 2007. 'Modelling the long-term cost-effectiveness of endovascular or open repair for abdominal aortic aneurysm.' *British Journal of Surgery* 95(2): 183–190.
- The EVAR Trial Participants. 2007. 'Patient fitness and survival after abdominal aortic aneurysm repair in patients from the UK EVAR trials.' *British Journal of Surgery* 94(6): 709–716.
- Brown, L.C., Brown, E.A., Greenhalgh, R.M., Powell, J.T., Thompson, S.G. 2010. 'Renal function and abdominal aortic aneurysm (AAA): the impact of different management strategies on long-term renal function in the UK EndoVascular Aneurysm Repair (EVAR) Trials.' *Annals of Surgery* 251(5): 966–975.
- Brown, L., Greenhalgh, R., Kwong, G., Powell, J., Thompson, S., Wyatt, M. 2007. 'Secondary interventions and mortality following endovascular aortic aneurysm repair: device-specific results from the UK EVAR Trials.' *European Journal of Vascular and Endovascular Surgery* 34(3): 281–290 Epub 15 June.
- Powell, J.T., Brown, L.C., Greenhalgh, R.M., Thompson, S.G. 2008. 'The rupture rate of large abdominal aortic aneurysms is this modified by anatomical suitability for endovascular repair?' *Annals of Surgery* 247(1): 173–179.
- Brown, L.C., Greenhalgh, R.M., Powell, J.T., Thompson, S.G. 'Use of baseline factors to predict complications and reinterventions after endovascular repair of abdominal aortic aneurysm.' *British Journal of Surgery* 97(8): 1207–1217.

## Context

EVAR first came to attention in 1991 and was pioneered by Volodos et al. (1991) in Ukraine and Parodi et al. (1991) in Argentina. The first report on the use of EVAR in the emergency situation was published in 1994 (Yusuf et al.). Between 1991 and 1996 there was increasing evidence that a commercial interest in this technique was emerging as various companies tried to make an appropriate commercial device. In this context, it became clear that a trial would be necessary and the team proposed such a trial in 1996 and made plans to apply for funding which was ultimately awarded by the HTA in 1999.

Four other trials have been conducted internationally addressing the question investigated in the EVAR 1 trial: the comparison of EVAR to open repair. However, no other trials have been conducted echoing the EVAR 2 study: that is, comparing EVAR to medical management for those unfit to undergo open repair. The other four trials conducted comparable to EVAR 1 are summarised below:

*The Dutch Randomised Endovascular Aneurysm Management (DREAM) trial:* A trial using a similar protocol to EVAR 1 based in the Netherlands, based on 351 patients across 24 Dutch and 4 Belgian hospitals. Started soon after the EVAR trials, this study has published results on operative mortality and longer-term outcomes (Prinssen et al. 2005 De Bruin et al. 2010).

*The French Anévrisme de l'aorte abdominale, Chirurgie versus Endoprothèse (ACE) trial:* This study began in 2003 but closed in 2008 after only recruiting just over 300 patients. The difficulty in recruitment was perhaps partly due to the results from EVAR 1 and DREAM which had by then been released, showing favourable 30-day mortality rates. The results, in contrast to the other three trials, suggested no difference in operative mortality between the open and the endovascular repair arms, 0.6 per cent versus 1.2 per cent, respectively (Becquemin et al. 2011).

*Open Versus Endovascular Repair (OVER) trial:* A US trial recruiting across 43 centres through the Veterans Affairs program, this study looked at a slightly younger fitter population than the EVAR trial between 2002 and 2008, with operative mortality and 2-year outcomes were published in 2009 (Lerderle et al. 2009) and long-term results released in 2012 (Lerderle et al. 2012). The study found no significant difference in the primary outcome of long-term all-cause mortality between the EVAR and open repair, with the short term survival advantage seen for EVAR fading over the long term.

### *Findings of the study*

The primary outcome studied was mortality (operative, all-cause and AAA related). In 2004, the first results of the study were published covering 30-day mortality, in which EVAR performed better, with rates of 1.8 per cent compared to 4.3 per cent for open repair (EVAR Trial Participants 2004). However, this clear benefit was lost over longer timescales as shown by results published in 2005 which showed no significant difference in all-cause mortality between the two groups over two years (EVAR Trial Participants 2005a). The EVAR procedure was more expensive than open repair (mean difference £1,177) and given the lack of any difference in outcomes, was not found to be cost-effective, but the model was sensitive to specific assumptions (Brown et al. 2012). The study also looked at outcomes over the longer term. Using a measure designed to determine aneurysm related (rather than all cause) mortality, EVAR performed better than open repair over the first five years of follow up, but at around six years post-operative, the differences between the groups become insignificant. The study has so far followed up patients to 10 years and has found that aneurysm related mortality is similar for both groups over that timescale (UK EVAR Trial Investigators 2010). In EVAR 2, the 30-day operative mortality was 7.3 per cent in the EVAR group, but the EVAR group later demonstrated a significant advantage in terms of AAA-related mortality, but this became apparent only after four years (EVAR Trial Participants 2005b; UK EVAR Trial Investigators 2010b). However, this advantage did not result in any benefit in terms of all-cause mortality and overall, since EVAR was more expensive than no intervention (mean difference £10,222) it was not found to be cost-effective (Brown et al. 2012).

The HTA has now funded the study team to continue to monitor the cohort for 15 years. None of the other three large trials conducted have followed up for this length of time so the study is significant in terms of looking at the long term outcomes following EVAR compared to alternative treatment approaches and potential long term complications.

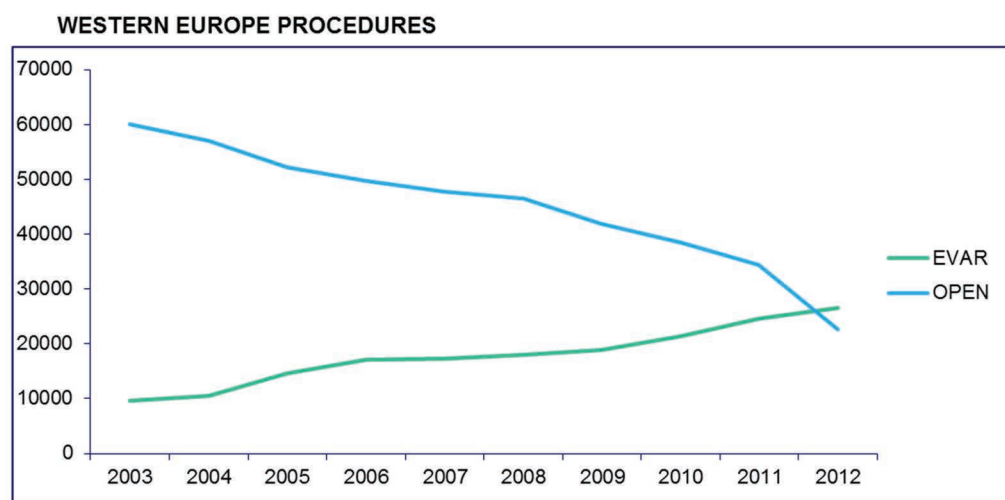
The key contribution of this study therefore is to show whether EVAR is safe over the long term. Although it is not found to be cost effective in these studies when looking at mortality as a key outcome, it is still being used more widely as it is preferred by patients. This is because it is less painful, and can be done under local anaesthetic – it is not major surgery in the same way as open repair. So given this preference and that EVAR is likely to be increasingly used for other reasons, such as commercial pressures, it is important to confirm whether it is stable and reliable over the long term.

Training is required to conduct the procedure. As part of the trial, they looked at the number of operations needed as part of the training procedure and the team think that this number is around 30–40 operations. This means an investment in training is required for effective implementation. However, given that the operations are increasingly being carried out in a limited number of high volume centres nationally, this is becoming less problematic.

### Impact

The usage of EVAR has increased dramatically, with evidence of a spike in use coincident with the publication of the key results from this study (in 2004, 2005 and 2010), as shown in Figure 1 below. Now over half of such operations are carried out using EVAR in the UK.

Figure 1 European Vascular and Endovascular Monitor (EVEM) data showing number of procedures using EVAR or open repair, 2003-2012. Source: BIBAMedTech Insights



### Y-O-Y GROWTH RATE

	2003-04	2004-05	2005-06	2006-07	2007-08	2008-09	2009-10	2010-11	2011-12
EVAR	9%	39%	18%	1%	4%	4%	14%	15%	8%
Open	-5%	-9%	-5%	-4%	-3%	-10%	-8%	-11%	-34%

EVAR trial 30-day results – The Lancet

EVAR 5-year results – The Lancet

EVAR 10-year results – NEJM

NICE Interventional Procedure Guidance (NICE 2006a) states that ‘current evidence on the efficacy and short-term safety of stent–graft placement in abdominal aortic aneurysm appears adequate to support the use of this procedure’ (p1) based largely on the EVAR data, supplemented by a systematic review. The guidance calls for more data on long term outcomes. Similarly, a NICE technology appraisal (NICE 2009a) suggests that ‘Endovascular stent–grafts are recommended as a treatment option for patients with unruptured infra-renal abdominal aortic aneurysms, for whom surgical intervention (open surgical repair or endovascular aneurysm repair) is considered appropriate’ (p1), echoing the findings of the EVAR study. Here, EVAR 1 was one of four trials used as evidence on EVAR as compared to open repair, EVAR 2 was the only evidence around the comparison to non-surgical management. EVAR was one of two main sources of economic data.

According to an interview conducted with a member of the study team, this study in particular was influential for three main reasons. Firstly, it is the only one of the four large-scale studies of EVAR that included long-term follow up to measure the reliability of EVAR over 10 years and more. Secondly, it is the only study from that group that looked at patients who were not fit for open repair, but that may be fit for EVAR. Finally, the economic analysis that was included made the study particularly useful in considering the implementation of the treatment in the UK health system.

The team that conducted the EVAR study has now received the data from the other three trials that have been conducted and have been funded to conduct an individual patient meta-analysis across all four trials. They hope that this larger data set will allow them to look in more detail at when and how complications occur to try and understand how the risk of complications can be minimised.

## NACHBID case study: neuroleptics in the treatment of aggressive challenging behaviour for people with intellectual disabilities

### *Description of the study*

The NACHBID trial looked at three different interventions for the treatment of aggressive challenging behaviour in adults: haloperidol, risperidone and a placebo (Tyrer et al. 2009). Haloperidol is a typical neuroleptic drug that was the most common comparator used in trials of first- and second-generation neuroleptic drugs at the time and was approved for the treatment of aggressive behaviour. However, at the time of the trial, risperidone was the most commonly prescribed medication for the treatment of aggressive challenging behaviour for people with intellectual disability (Tyrer et al. 2009). According to a key informant interview, the standard of care for treating challenging behaviour in people with intellectual disability at the time of the trial was to give medication, particularly antipsychotic drugs, because they were the most widely used and appeared most effective. (Interview Data). According to Tyrer et al. (2009), a near to consensus definition of challenging behaviour is, 'any culturally abnormal behaviour(s) of such intensity, frequency or duration that the physical safety of the person or others is likely to be placed in serious jeopardy or behaviour which is likely to seriously limit use, or result in the person being denied access to, ordinary community facilities.' (Tyrer et al. 2009, p3).

The total cost of the study reported by the HTA is £630,943 (NICE 2014). However, according to a key informant interview, the total cost of the study was closer to £800,000 if one takes into account the extra cost of extending the recruitment period by an extra 18 months (Interview Data).

The findings of the NACHBID trial were first published in the *Lancet* in 2008 and then in the National Institute for Health Research's Journal, *Health Technology Assessment*, in April 2009 (Tyrer et al. 2008; 2009). The later report includes a full economic analysis of the cost-effectiveness of the three interventions.

### *Context*

The lifetime prevalence of aggressive challenging behaviour among those with intellectual disability is up to 60 per cent and aggression is estimated to cost the NHS and social services around £50 million to £140 million per year (Tyrer et al. 2009). At the time of the trial, antipsychotics were commonly prescribed for the treatment of challenging behaviour in people with intellectual disabilities, despite little evidence of their effectiveness in this patient group. According to a key informant interview, the limited evidence that did exist was almost entirely funded by the pharmaceutical industry (Interview Data). At the time that the study was conducted, the National Institute for Clinical Excellence (NICE) guidelines approved the use of typical neuroleptic drugs as first-line treatment for challenging behaviour in adults with intellectual disability but did not give clear guidance as to whether these typical neuroleptics should be used preferentially over the older drugs, referred to as 'first-generation' neuroleptic drugs. According to an interviewee from the research team, the guidance at the time was that chlorpromazine was allowed to be given and that there was no question that the prescription of antipsychotic drugs was an unusual practice in this population (Interview Data).

Prior to the NACHBID trial, there had only been one systematic review of the use of neuroleptic drugs in the treatment of challenging behaviour in people with intellectual disability (Brylewski and Duggan 1999). The review found eight randomised controlled trials that compared neuroleptic medications to placebo and concluded that the trials did not show any evidence that neuroleptics are effective treatment for challenging behavior in adults with intellectual disability. According to a key informant interview, Sir Michael Rawlins, the head of NICE at the time, specifically highlighted the lack of evidence of effectiveness of neuroleptics at the time of the study (Interview Data).

The research team were not aware of any ongoing work on the use of antipsychotics to treat challenging behaviour in patients with intellectual disability at the time of conducting the study (Interview Data). According to an interviewee, the challenge of recruiting patients with intellectual disability into trials, which the NACHBID research team also found challenging, may have been a contributing factor to the relatively poor evidence of effectiveness of treatment for this patient group. The interviewee stressed that researchers face tremendous difficulty recruiting patients with intellectual disability because they have to get assent, rather than consent, from a carer or other appropriate individual because they may not want to give consent or may not feel able to give consent (Interview Data).

According to a member of the project team, the main reason for carrying out this work on the use of neuroleptics for challenging behaviour was the poor evidence base (Interview Data). The NACHBID trial was designed to address this deficiency of evidence by comparing the effectiveness and cost-effectiveness of two neuroleptics with a placebo in a randomised controlled clinical trial (Tyrer et al. 2009).

### *Findings of the study*

The NACHBID trial looked at the effectiveness of the three interventions on aggressive challenging behaviour over four weeks. The two main findings that emerged from the study were that patients in all three treatment groups improved within a week of receiving treatment and that the improvement was greatest in the placebo group. This effect was maintained over a four-week period. The patients receiving the placebo showed 79 per cent aggression decline after four weeks compared to 57 per cent for the neuroleptics. However, the effectiveness of the placebo was not statistically significant ( $p=0.06$ ). According to a key informant interview, the research team concluded that the placebo reaction likely resulted from the actual giving of the tablet, additional attention given and monitoring (Interview Data). Nevertheless, the study demonstrated that there is no evidence that either haloperidol or risperidone are superior to placebo in either the short or the medium term and that placebo is most effective over a four week period, although the difference was not statistically significant.

The findings from the economic analysis showed that placebo is the most cost-effective treatment for aggressive challenging behaviour in patients with intellectual disability (Tyrer et al. 2009). The research team conducted a cost-effectiveness and cost-utility analysis using three outcome measures: total costs, modified overt aggression scale (MOAS) and quality of life questionnaire (QOL-Q) as the main outcome measures. The mean total costs of treatment for the three groups were: £16,336 for placebo, £17,626 for haloperidol and £18,954 for risperidone. The incremental cost-effectiveness ratio (ICER) for haloperidol relative to placebo was £625 per additional point difference on the MOAS and the ICER for risperidone relative to placebo was £1,245 per additional point difference on the QOL-Q. Using a cost-effectiveness

acceptability curve to determine the probability that either haloperidol or risperidone would be cost-effective, the authors found that there was a 50 per cent probability that haloperidol is cost-effective if society is not willing to pay anything for improvement in MOAS scores and there is an 89 per cent probability that haloperidol is cost-effectiveness if society is willing to pay a substantial amount, £3,000, per point increase in MOAS score. Similarly, the study found that there is a 22 per cent probability that risperidone is cost-effective if society is not willing to pay anything for improvement in quality of life and this probability does not increase for higher willingness-to-pay thresholds.

### *Impact*

The main source for information on the impact of this work was a key informant interview with a member of the study team. This interviewee described how the main benefit of this trial is for individuals with intellectual disability. They suggested that patients with intellectual disability are now prescribed fewer antipsychotic drugs for treatment of challenging behavior (Interview Data) and that there has been a 50 per cent reduction in the prescribing of these drugs in the UK since 2008, when the research team first published their results. The interviewee noted that a further benefit to patients from the reduction in antipsychotic prescribing behaviour is also the consequent reduction in negative side effects of the medication. For example, a common side effect of antipsychotic drugs is stimulation of the appetite, which leads to weight gain and metabolic syndrome, which predisposes patients to diabetes and other problems related to having excess fat in the blood (Interview Data).

Another benefit of the trial noted at interview was a renewed interest in psychological treatment (Interview Data). At the time that the trial was conducted, psychological treatment was not commonly recommended for treatment of challenging behaviour in patients with intellectual disability because the prescribing of medication was perfectly acceptable at that time and was considered to be adequate treatment. According to the same interviewee, following the NACHBID trial, there have been several studies on the effectiveness of psychological treatments in this population and there have been posts set up to coordinate improvements in psychological interventions.

The interviewee described how the NACHBID trial results were widely disseminated both within the UK and internationally. The *Lancet* paper by Tyrer et al. 2008 has also been widely cited in the literature, with google reporting that it has been cited 171 times (up to 22 April 2014). The wide dissemination of the study results have likely contributed to the observed impact of the study.

The interviewee also suggested that the NACHBID trial has likely also had an impact on research in the field of intellectual disability (Interview Data). The same interviewee noted that the NACHBID study demonstrated that the rules of science and evidence-based medicine apply just as much to intellectual disability as they do to the rest of medicine and psychiatry.

According to the key informant interview, the main challenges to implementation of the NACHBID trial's findings are the preconceived opinions of people that work in intellectual disability (Interview Data). The same interviewee reported that the research team noted resistance among this group to their findings. Some individuals working in the field felt that they had better knowledge of treatment effectiveness because of their experiences working with this patient group than the NACHBID research

team. However, the interviewee concluded that given the significant decline in the prescribing of antipsychotics within this patient group, it is unlikely that this view is widely held.

A major facilitator for implementation of the study's findings is the NIHR's HTA journal and NICE. According to a key informant interview, the NACHBID trial, together with more recent studies in the same area, collectively resulted in the creation of a NICE project team on challenging behaviour and learning disabilities in April 2013, which is in the process of developing guidance on the treatment of challenging behaviour in patients with intellectual disability (NICE 2014). The revised guidelines are set to be published in May 2015. According to the same key informant interview, the guidelines will almost certainly recognise the benefits of psychological treatment and the ineffectiveness of drug treatment (Interview Data). The interviewee concluded that the likely future impact of the trial will be the ongoing impact on patients and the impact on the forthcoming NICE guidance on challenging behaviour in patients with intellectual disability.



## PACMAN case study. An evaluation of the clinical and cost-effectiveness of pulmonary artery catheters in patient management in intensive care: a systematic review and a randomised controlled trial

### *Description of the study*

A pulmonary artery catheter (PAC) is a device which is used in intensive care units (ICU) to monitor patients, measuring pressure in the heart and lung blood vessels. The catheter is directly inserted through the pulmonary artery through a large blood vessel in the neck or groin and as such is an invasive technique. The study consisted of a systematic review, followed by a multi-centre, randomised controlled trial including economic evaluation (both cost-utility and cost-effectiveness analysis), to investigate both the clinical and cost effectiveness of managing critically ill patients in adult general intensive care with or without PACs. The comparator group were managed without a PAC but had the option of using alternative cardiac output monitoring devices, though this was not specified and in many cases no alternative would have been used. All adult patients in participating ICUs deemed by the responsible treating clinician to require management with a PAC were eligible participants, and the main outcome measure used was hospital mortality.

The study was conducted between January 2000 and September 2006, and received £764,327 in funding from the HTA Programme. The project was led by Chief Investigator Professor Kathryn Rowan from the Intensive Care National Audit and Research Centre. In addition to a HTA report (Harvey et al. 2006), the following twelve additional publications resulted from the study:

- Harvey, S., Harrison, D.A., Singer, M., Ashcroft, J., Jones, C.M., Elbourne, D., Brampton, W., Williams, D., Young, D., Rowan, K., on behalf of the PAC-Man study collaboration. 2005. 'Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial.' *Lancet* 366(9484): 472–477.
- Harvey, S. 2004. 'Big academic randomised controlled trial completed: PAC-Man Study update.' *Journal of the Intensive Care Society* 5(3): 95.
- Harvey, S.E., Elbourne, D., Ashcroft, J., Jones, C.M., Rowan, K. 'Informed consent in clinical trials in critical care: experience from the PAC-Man study.' *Intensive Care Medicine* 32(12): 2020–2025.
- Harvey, S., Singer, M. 2006. 'Managing critically ill patients with a pulmonary artery catheter.' *British Journal of Hospital Medicine* 67(8): 421–426.
- Harvey, S., Singer, M. 'PAC-Man study - what you should know!' *Journal of the Intensive Care Society* 4(2): 46.
- Harvey, S.E., Welch, C.A., Harrison, D.A., Rowan, K.M., Singer, M. 'Post hoc insights from PAC-Man - The U.K. pulmonary artery catheter trial.' *Critical Care Medicine* 36(6): 1714–1721.
- Harvey, S., Young, D., Brampton, W., Cooper, A.B., Doig, G., Sibbald, W., Rowan, K. 2006. 'Pulmonary artery catheter for adult patients in intensive care (review).' *Cochrane Database of Systematic Reviews* CD003408.

- Harvey, S., Young, D., Rowan, K., Brampton, W., Cooper, A.B., Doig, G. 2001. 'Pulmonary artery catheters for adult intensive care patients.' Reference: *Cochrane Database of Systematic Reviews* CD003408.
- Harvey, S., Young, D., Brampton, W., Cooper, A.B., Doig, G., Sibbald, W., Rowan, K. 2006. 'Pulmonary artery catheters for adult patients in intensive care.' *Anesthesia & Analgesia* 103(6): 1577.
- Young, J.D. 'Right heart catheterization in intensive care.' *British Journal of Anaesthesia* 86(3): 327–329.
- Stevens, K., McCabe, C., Jones, C., Ashcroft, J., Harvey, S., Rowan, K. 'The incremental cost effectiveness of withdrawing pulmonary artery catheters from routine use in critical care.' *Applied Health Economics and Health Policy* 4(4): 257–64.
- Stevens, K., McCabe, C., Jones, C., Ashcroft, J., Harvey, S., Rowan, K., on behalf of the PAC-Man Study Collaboration. 2006. 'The incremental cost effectiveness of withdrawing pulmonary artery catheters from routine use in critical care.' *Applied Health Economics and Health Policy* 4(4): 257–64.

## Context

At the time this study was proposed, the use of PACs had gradually become the standard of care over the previous 30 years since their introduction for crucially ill patients, despite no clear evaluative evidence of clinical or cost effectiveness of the treatment. Although there was variation in the levels of use, many institutions were using them in every critically ill patient in intensive care.

The topic was identified by the study team through a consensus process (Vella et al. 2000; Goldfrad et al. 2000). The consensus process consisted of a survey of healthcare professionals in the field to identify and prioritise important research topics. The work was the first academically funded RCT in critical care in the UK and as such the team decided to conduct a consensus based exercise to identify this topic for the work. The topic of PACs came top of that list. PACs are very controversial and have polarised medical opinion (Robin 1988; Dalen and Bone 1996; Vincent et al. 1998; Pulmonary Artery Catheter Conference Participants 1997). Proponents cite its ability to allow accurate measurement of cardiac output and other haemodynamic variables, improving diagnosis and management of circulatory instability (Vincent et al. 1998; Pulmonary Artery Catheter Conference Participants 1997). By contrast, critics of the technique cite potential complications associated with its insertion and use (Robin 1988; Bowdle 2002; Coulter 1999), inaccuracies in measurement, poor interpretation of data (Iberti et al. 1990; 1994; Gnaegi et al. 1997) and the lack of positive outcome benefits Gore et al. 1987; Zion et al. 1990).

PACs may have been identified partly because of the recent publication of a large non-randomised, risk-adjusted study which rekindled the long-standing debate about the clinical effectiveness of PACs (Connors et al. 1996). The study suggested that the use of a PAC led to an increased risk of death within 20 days of admission to an ICU. An earlier systematic review had also shown that there was very little evidence from RCTs on the effectiveness of PACs (Cooper et al. 1996). This study updates that systematic review to consider the need for an RCT, and initial searching of the literature (to June 2001) identified only one small RCT of general intensive care patients (Guyatt 1991). This particular study had

been prematurely discontinued, and all of the other (seven) studies identified focused on high-risk surgery patients. As such, the need for an RCT was clear and the team proceeded to carry out that trial.

The time from the initial consensus exercise to carrying out the RCT was therefore fairly lengthy, so although the need for an RCT was still indicated, by the time the study was completed there had already started to be some change in practice, and the use of PACs had started to wane, perhaps partly because of the observational study results suggesting that PACs may be harmful.

### *Findings of the study*

The study found that there was no statistically or clinically significant difference in levels of hospital mortality for patients treated using a PAC compared to those without. Other secondary outcome measures such as the median length of stay in ICU or in an acute hospital also showed no benefit. In addition, economic analysis showed that the expected cost per QALY gained from the withdrawal of PAC was £2,985: well within the bound of cost-effectiveness. These findings are potentially applicable to any ICU where PACs are used. Because the required change in practice is just the removal of an unhelpful and unnecessary technique, no training is required to make the change, short of informing medical professionals of the changes in best practice. Therefore, from an implementation point of view these findings are simple to implement in an NHS context.

### *Impact*

The study had an immediate impact directly through the work conducted in the study itself. The systematic review conducted through the study was the first in a new ongoing Cochrane review which the group involved, and other interested parties since, are maintaining and updating on a regular basis (Harvey et al. 2006b). This ensures that the research in the area is monitored in an ongoing manner and an overview of the best evidence on the topic remains available to inform policy and practice.

Through the Cochrane review, the evidence from the study was made available to inform practice through a Cochrane Quality and Productivity topics article (NICE 2006b). This is a series developed by NICE which is intended to raise awareness in the NHS of practices which, based on a Cochrane review of the evidence, could be significantly reduced, or completely stopped without negatively affecting the quality of care, thus saving money or resources.

The study has not, however, been cited on any specific NICE guidance, largely because there is little by way of NICE guidance in this area on which the study could be cited. The team used alternative approaches to disseminate the findings to practitioners. As the centre at which the study was conducted combines both audit and research functions, the team have close contact with all the critical care units in the country, as they audit them regularly. The work was presented at their annual meeting and the findings distributed through this network. The findings were also presented as a plenary session at the International Symposium on Intensive Care and Emergency Medicine in Brussels. The work was also cited in the surviving sepsis guidance as part of the evidence for their recommendation 'against the routine use of the pulmonary artery catheter for patients with sepsis-induced ARDS' (Surviving Sepsis Campaign 2012, p602).

By the time this study was published, there had already been a fall in the use of PACs, perhaps partly due to the publication of the previous, non-randomised study (Connors 1996). However, there was a continued reduction in use. The CI suggested that the study was perhaps the ‘final nail in the coffin’ for PACs. The economic analysis in particular was novel and may have helped to support the decline in NHS use of PACs. The use of mortality as primary outcome measure may have also been helpful as it is a very objective measure.

A final important impact of this study was its role as a landmark trial in critical care. It was the first time that an RCT had been conducted in the field, and it showed that it could be done and it could be argued that it paved the way for further studies in the field, and its increasing academic recognition. The study provided the beginnings of a research network across critical care centres and further trials have since been conducted, such as TracMan (Young et al. 2013) which followed shortly after this work and other subsequent studies. As such, it could be argued that the study was important in paving the way for further HSR trials in critical care.

## DiGEM case study. Blood glucose self-monitoring in Type 2 diabetes: a randomised controlled trial

### *Description of the study*

The aim of the DiGEM study was to investigate the use of self-monitoring of blood glucose (SMBG) amongst people with Type 2 diabetes who were not using insulin to regulate blood glucose. The aim was to determine whether SMBG, alone, or alongside additional instruction of the implications of the monitoring and how it can be incorporated into self-care, is more effective than standard care in improving glycaemic control in this group. Standard of care typically consists of a range of medications and lifestyle advice. Large trials have confirmed the effectiveness of intensive glycaemic control in reducing complications that can result from diabetes, and tight glycaemic control can be achieved by means of lifestyle changes and medications.

The study was conducted between October 2002 and March 2009, led by Chief Investigator Professor Andrew Farmer from the University of Oxford. The project was supported by the HTA Programme which provided £ 619,204.00 in research funding for the work. The work was published in the *HTA* journal (Farmer et al. 2009) and resulted in six additional publications in other peer reviewed journals:

- Simon, J., Gray, A., Clarke, P., Wade, A., Neil, A., Farmer, A. 2008. 'Cost effectiveness of self-monitoring of blood glucose in patients with non-insulin treated Type 2 diabetes: economic evaluation of data from the DiGEM trial.' *BMJ* 336(7654): 1177–1180.
- Farmer, A., Wade, A., Goyder, E., Yudkin, P., French, D., Craven, A., Holman, R., Kinmonth, A.L., Neil, A. 2007. 'Impact of self-monitoring of blood glucose in the management of patients with non-insulin treated diabetes: open parallel group randomised trial.' *BMJ* 335(7611): 132.
- Farmer, A., Neil, A. 2005. 'In response to 'variations in glucose self-monitoring during oral hypoglycaemic therapy in primary care' (letter). *Diabetic Medicine* 22(4): 511–512.
- Farmer, A., Perera, R., Ward, A., Heneghan, C., Oke, J., Barnett, A., Davidson, M., Guerci, B., Coates, V., Schwedes, U., O'Malley S. 2012. 'Meta-analysis of individual patient data in randomised trials of self-monitoring of blood glucose in people with non-insulin treated Type 2 diabetes.' *BMJ* 344:e486
- Farmer, A., Wade, A., French, D.P., Goyder, E., Kinmonth, A.L., Neil, A. 2005. 'The DiGEM trial protocol - a randomised controlled trial to determine the effect on glycaemic control of different strategies of blood glucose self-monitoring in people with Type 2 diabetes.' *BMC Family Practice* 6(25): 6–25.
- Farmer, A., Neil, A. 2005. 'Variations in glucose self-monitoring during oral hypoglycaemic therapy in primary care.' *Diabetic Medicine* 2004;22(4): 511–512.

### *Context*

Self-monitoring of blood glucose (SMBG) was originally developed for use in Type 1 diabetes to support insulin dose adjustment. It is also generally accepted practice for insulin-treated patients with Type 2 diabetes. However, the rationale for SMBG among non-insulin-treated patients with Type 2 diabetes is

less clear. Despite this, at the time this work was proposed, SMBG was widely accepted practice, and was frequently incorporated into self-management interventions of diabetes (Blonde 2002; European Diabetes Policy Group 1999). Use of SMBG in this context had led to major and increasing costs to the health care budget, largely through the consumable test strips these devices use (Davidson 2005; Farmer and Neil 2004), as the prevalence of Type 2 diabetes in the UK grew dramatically. Between 1996 and 2009, the number of people diagnosed with the condition has increased from 1.4 to 3 million (Diabetes UK 2013) and by 2010 the amount spent on blood glucose testing strips in England in primary care was approximately £150m. By comparison, approximately £300m was spent on insulin and £250m on anti-diabetic drugs (Diabetes UK 2013; NHS Information Centre 2011).

Prior to this study, few large-scale trials of SMBG had been conducted. Systematic reviews on the topic identified mostly small-scale trials, and had found that self-monitoring was no more effective in improving glycaemic control than urine testing or measurement of HbA1c for people with Type 2 diabetes (Coster et al. 2000; Faas et al. 1997). A number of observational studies had been conducted with mixed results, but these were hampered by the challenge of untangling the relationship between attitudes towards self-care and the use of SMBG (Martin et al. 2006). This study was in particular motivated by the evidence synthesis by Coster and colleagues which was commissioned by the HTA (Coster 2000). They found that there was no evidence of benefit from self-monitoring, but that the evidence available was insufficient to exclude either an appreciable beneficial effect or a small adverse effect because ‘the studies included were generally poorly reported and lacking in statistical power’. They conclude, in agreement with the findings of another evidence synthesis (Faas et al. 1997), that ‘a large randomized trial of the effect of blood glucose self-monitoring in Type 2 diabetes is desirable’.

### *Findings of the study*

The study was a randomised controlled trial in which 453 people were individually randomised to one of three treatment options:

- Standardised usual care with 3-monthly blood glucose testing (control, n = 152).
- Blood glucose self-testing with patient training focused on clinician interpretation of results in addition to usual care (less intensive self-monitoring, n = 150).
- SMBG with additional training of patients in interpretation and application of the results to enhance motivation and maintain adherence to a healthy lifestyle (more intensive self-monitoring, n = 151).

As is evident from the three groups, the researchers took particular care to ensure that there was no confounding of the results through additional education being provided to those patients receiving the blood glucose monitors.

The findings suggested that the long-term health benefits in terms of the primary outcome (blood glucose levels at 12 months) of using blood glucose monitoring were at best small (less than 0.2 per cent), and not statistically significant, nor likely to be clinically important. Furthermore, looking at quality of life, there appears to be an initial negative impact of SMBG which outweighed any potential benefits resulting from the lower levels of risk factors achieved at the end of trial follow-up. The study also showed that SMBG was considerably more expensive than standard of care, by £92 and £84 for the less intensive SMBG and

the more intensive SMBG groups respectively. Results of the extrapolation also suggested that the incremental lifetime savings in diabetes complications did not offset the additional intervention costs. Cost utility-analysis was also conducted using a conservative approach, with no long-term treatment effects assumed beyond the one year follow up at the end of the intervention. The analysis showed that it is unlikely that either intervention tested is cost-effective compared to standard of care.

These findings are potentially relevant to all patients with Type 2 diabetes who are not using insulin. There are around 3 million people with Type 2 diabetes in the UK, and of these only around 20 per cent are on insulin, so the applicability of these findings is potentially very broad.

From an implementation point of view, these findings are easy to adopt. Other than providing the information to doctors that these devices should not be used, no additional training is needed to implement these findings. However, in practice, there were some challenges associated with putting these findings into practice. A strong industry lobby continued to push back on these findings and worked to try and convince GPs that monitoring was a necessary part of treatment practice.

### *Impact*

The most recent diabetes guidance was published by NICE in 2009, before the final report of the DIGEM study was released and as such does not directly reflect these findings. The guidance suggests that doctors should 'offer self-monitoring of plasma glucose to a person newly diagnosed with Type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon' (NICE 2009b, p6).

Following the study there was still some significant controversy regarding the use of SMBG in type 2 diabetes, and to try and address this some of the members of the DIGEM study team developed a meta-analysis of the results of the five large trials of SMBG that had been published since 1999. They accessed the original data sets and re-analysed across the whole sample, giving an overall sample of 2000 people. The findings of this research were published in 2012 and confirmed the findings of the DIGEM study, showing that any health benefits from SMBG were small. Additionally, because of the sample size they were able to look at subgroups within the population and found no evidence that particular subgroups would benefit from SMBG (Farmer et al. 2012).

The NICE guidance on diabetes, including SMBG, is currently under review with revised guidance scheduled for publication in Aug 2015. Amongst topics under review is 'Self-monitoring of blood glucose levels (finger pricks)'. This will include: 'Targets; Frequency of monitoring; Timing; Site of testing'; and the review question is 'Should self-monitoring be used to manage blood glucose levels in people with Type 2 diabetes?' (NICE 2012, p8 and p12)<sup>11</sup> It is expected that the revised guidance will reflect the findings of this work.

IDF guidance also uses evidence from the DIGEM study alongside studies from across a number of countries to form its recommendation that 'SMBG should only be used when individuals with diabetes (and/or their caregivers) and/or their healthcare providers have the knowledge skills and willingness to

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<sup>11</sup> <http://guidance.nice.org.uk/CG/Wave0/612>

incorporate SMBG monitoring and therapy adjustment into their diabetes care plan in order to attain agreed treatment goals' (International Diabetes Federation 2009).

The HTA Programme has also since conducted further work in this area, through a systematic review published in 2010 (Clar et al. 2010). The review identified 30 RCTs, although few were of high quality. Although they identified some studies asserting that SMBG may lead to savings in healthcare costs, which may offset the costs of testing, they considered the DIGEM study to be the best analysis to date. They identified a number of qualitative studies which showed that there was a lack of education in how to interpret and use the data from SMBG, and that failure to act on the results was common. The review concluded that the evidence suggests that SMBG is of limited clinical effectiveness in improving glycaemic control in people with Type 2 diabetes on oral agents, or diet alone, and is therefore unlikely to be cost-effective.



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