*Health Technology Assessment* 2009; Vol. 13: No. 7

# Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients

G Mowatt, G Houston, R Hernández, R de Verteuil, C Fraser, B Cuthbertson and L Vale

January 2009
DOI: 10.3310/hta13070


**Health Technology Assessment**
**NIHR HTA Programme**
**www.hta.ac.uk**



**How to obtain copies of this and other HTA Programme reports.**
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

**Contact details are as follows:**

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can be purchased only for the current or forthcoming volume.

**Payment methods**

*Paying by cheque*
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

*Paying by credit card*
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

*Paying by official purchase order*
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

**How do I get a copy of *HTA on CD*?**

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

---

The website also provides information about the HTA Programme and lists the membership of the various committees.

# Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients

G Mowatt,[1] G Houston,[3] R Hernández,[2] R de Verteuil,[1,2] C Fraser,[1] B Cuthbertson[1,3] and L Vale[1,2*]

[1]Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[2]Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[3]NHS Grampian, UK

*Corresponding author

**Declared competing interests of authors:** none

Published January 2009
DOI: 10.3310/hta13070

This report should be referenced as follows:

Mowatt G, Houston G, Hernández R, de Verteuil R, Fraser C, Cuthbertson B, Vale L. Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients. *Health Technol Assess* 2009;**13**(7).

*Health Technology Assessment* is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (*SciSearch*®) and *Current Contents*®/Clinical Medicine.

# NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the effectiveness, costs and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined as all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, from the public and consumer groups and from professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Second, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Third, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer reviewed by a number of independent expert referees before publication in the widely read journal series *Health Technology Assessment*.

**Criteria for inclusion in the HTA journal series**

Reports are published in the HTA journal series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this issue of the journal was commissioned and funded by the HTA Programme on behalf of NICE as project number 07/20/01. The protocol was agreed in April 2007. The assessment report began editorial review in August 2007 and was accepted for publication in June 2008. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.



ISSN 1366-5278



Published by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk), on behalf of NCCHTA.

Printed on acid-free paper in the UK by the Charlesworth Group.

T

# Abstract

## Systematic review of the clinical effectiveness and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients

G Mowatt,[1] G Houston,[3] R Hernández,[2] R de Verteuil,[1,2] C Fraser,[1] B Cuthbertson[1,3] and L Vale[1,2*]

[1]Health Services Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[2]Health Economics Research Unit, Institute of Applied Health Sciences, University of Aberdeen, UK
[3]NHS Grampian, UK

*Corresponding author

**Objectives:** To assess the effectiveness and cost-effectiveness of oesophageal Doppler monitoring (ODM) compared with conventional clinical assessment and other methods of monitoring cardiovascular function.

**Data sources:** Electronic databases and relevant websites from 1990 to May 2007 were searched.

**Review methods:** This review was based on a systematic review conducted by the US Agency for Healthcare Research and Quality (AHRQ), supplemented by evidence from any additional studies identified. Comparator interventions for effectiveness were standard care, pulmonary artery catheters (PACs), pulse contour analysis monitoring and lithium or thermodilution cardiac monitoring. Data were extracted on mortality, length of stay overall and in critical care, complications and quality of life. The economic assessment evaluated strategies involving ODM compared with standard care, PACs, pulse contour analysis monitoring and lithium or thermodilution cardiac monitoring.

**Results:** The AHRQ report contained eight RCTs and was judged to be of high quality overall. Four comparisons were reported: ODM plus central venous pressure (CVP) monitoring plus conventional assessment vs CVP monitoring plus conventional assessment during surgery; ODM plus conventional assessment vs CVP monitoring plus conventional assessment during surgery; ODM plus conventional assessment vs conventional assessment during surgery; and ODM plus CVP monitoring plus conventional assessment vs CVP monitoring plus conventional assessment postoperatively. Five studies compared ODM plus CVP monitoring plus conventional assessment with CVP monitoring plus conventional assessment during surgery. There were fewer deaths [Peto odds ratio (OR) 0.13, 95% CI 0.02–0.96], fewer major complications (Peto OR 0.12, 95% CI 0.04–0.31), fewer total complications (fixed-effects OR 0.43, 95% CI 0.26–0.71) and shorter length of stay (pooled estimate not presented, 95% CI –2.21 to –0.57) in the ODM group. The results of the meta-analysis of mortality should be treated with caution owing to the low number of events and low overall number of patients in the combined totals. Three studies compared ODM plus conventional assessment with conventional assessment during surgery. There was no evidence of a difference in mortality (fixed-effects OR 0.81, 95% CI 0.23–2.77). Length of hospital stay was shorter in all three studies in the ODM group. Two studies compared ODM plus CVP monitoring plus conventional assessment vs CVP monitoring plus conventional assessment in critically ill patients. The patient groups were quite different (cardiac surgery and major trauma) and neither study, nor a meta-analysis, showed a statistically significant difference in mortality (fixed-effects OR 0.84, 95% CI 0.41–1.70). Fewer patients in the ODM group experienced complications (OR 0.49, 95% CI 0.30–0.81) and both studies reported a statistically significant shorter median length of hospital stay in that group. No economic evaluations that met the inclusion criteria were identified from the existing literature so a series of balance sheets was constructed. The results show that ODM strategies are likely to be cost-effective.

**Conclusions:** More formal economic evaluation would allow better use of the available data. All identified

studies were conducted in unconscious patients. However, further research is needed to evaluate new ODM probes that may be tolerated by awake patients. Given the paucity of the existing economic evidence base, any further primary research should include an economic evaluation or should provide data suitable for use in an economic model.

# Contents

# List of abbreviations

| | |
|---|---|
| AHRQ | Agency for Healthcare Research and Quality |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CI | confidence interval |
| COMS | cardiac output monitoring system |
| CVP | central venous pressure |
| DARE | Database of Abstracts of Reviews of Effectiveness |
| ECRI | Emergency Care Research Institute |
| FDA | Food and Drug Administration |
| HDU | high dependency unit |
| HMIC | Health Management Information Consortium |
| HTA | Health Technology Assessment |
| ICER | incremental cost-effectiveness/ utility ratio |
| ICU | intensive care unit |
| IQR | interquartile range |
| LiDCO | lithium dilution cardiac monitor |
| NCCHTA | National Co-ordinating Centre for Health Technology Assessment |
| NHS EED | NHS Economic Evaluation Database |
| NICE | National Institute for Health and Clinical Excellence |
| NR | not reported |
| ODM | oesophageal Doppler monitoring |
| OR | odds ratio |
| PAC | pulmonary artery catheter |
| QALY | quality-adjusted life-year |
| RCT | randomised controlled trial |
| RR | relative risk |
| SCI | Science Citation Index |
| TAR | Technology Assessment Review |
| TECO | transesophageal cardiac output |
| WMD | weighted mean difference |

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

# Executive summary

## Description of proposed service

Oesophageal Doppler monitoring (ODM) measures blood velocity in the descending thoracic aorta using a flexible probe inserted into the patient's oesophagus. This information is combined with an estimate of aortic cross-sectional area (derived from a nomogram based on the patient's age, height and weight) allowing continuous monitoring of cardiac output and haemodynamic status. ODM is a relatively simple procedure, generally limited in use to a critical care or theatre setting, that requires no calibration and minimal training.

## Epidemiology and background

Optimal management of cardiac output, fluid balance and haemodynamic status is considered key to improving outcome in high-risk surgical and critically ill patients. Traditionally, pulmonary artery catheters (PACs) have been used to monitor cardiac output and haemodynamic status to guide treatment, but they have been shown to provide no benefit to this patient group.

Less invasive methods of monitoring cardiac output and other haemodynamic variables include ODM, transoesophageal echocardiography, transthoracic impedance, carbon dioxide elimination and systems based upon pulse contour analysis and dye dilution methods. These may be used alongside conventional clinical assessment which involves assessment of various clinical markers, e.g. heart rate, systolic blood pressure and urinary output, with or without a measure of blood flow or central venous pressure.

## Objective

To assess the effectiveness and cost-effectiveness of ODM, in comparison with conventional clinical assessment and other methods of monitoring cardiovascular function.

## Methods

A systematic review of studies of effectiveness and cost-effectiveness was conducted.

### Data sources

Searches of electronic databases [including MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) and the Cochrane Library] and relevant websites until May 2007 were undertaken to identify published and unpublished reports, including previous systematic reviews.

### Study selection

For the review of effectiveness, randomised controlled trials (RCTs), or systematic reviews of RCTs, assessing the effects of ODM in the target populations were identified. Comparator interventions considered were standard care, PACs, pulse contour analysis monitoring and lithium or thermodilution cardiac monitoring. Non-English language studies and studies reported only as abstracts were excluded.

For the review of economic evaluations studies had to compare, in terms of both costs and outcomes, strategies involving ODM compared with standard care, PACs, pulse contour analysis monitoring and lithium or thermodilution cardiac monitoring. No language restrictions or other limitations to searches were imposed.

### Data extraction

For the review of effectiveness a recent high-quality systematic review, conducted by the US Agency for Healthcare Research and Quality (AHRQ), was identified. A judgement was made to base this review on this study, supplemented by evidence from any additional studies identified. Data were extracted on mortality, length of stay overall and in critical care, complications and quality of life.

The quality of primary studies was assessed using the Emergency Care Research Institute (ECRI)

25-question quality scale. The systematic review was assessed using a 10-item checklist developed by Oxman and Guyatt. Where appropriate, meta-analysis was employed to estimate a summary measure of effect on relevant outcomes. Where a quantitative synthesis was considered to be inappropriate or not feasible, a narrative synthesis of results was provided.

## Economic modelling

Partial economic modelling exercises were explored for pairwise comparisons between strategies that used ODM and those that did not. Differences in mortality and length of stay were considered within these exercises. Where data allowed, probability distributions were attached to model parameters [e.g. lognormal probability distributions for odds ratios and normal distributions for length of hospital stay differences using information on the confidence intervals (CIs) surrounding point estimates], and probabilistic analyses were conducted. Costs were stated in £ sterling for 2006–7. Cost-effectiveness results were expressed in additional cost per additional quality-adjusted life-year (QALY), as well as the average extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective. For the former the results were presented in the form of incremental cost-effectiveness planes and for the latter the data were presented as histograms.

# Results

## Number and quality of studies and direction of evidence

The AHRQ report contained eight RCTs involving 757 adult patients. Two additional RCTs, involving 202 patients, were identified. Eight of these primary studies were judged to be of high quality and two were judged to be of moderate quality. The AHRQ report was judged to be of high quality overall. The 10 primary studies reported four comparisons (one study reported two):

- ODM plus central venous pressure (CVP) monitoring plus conventional assessment versus CVP monitoring plus conventional assessment during surgery
- ODM plus conventional assessment versus CVP monitoring plus conventional assessment during surgery
- ODM plus conventional assessment versus conventional assessment during surgery
- ODM plus CVP monitoring plus conventional assessment versus CVP monitoring plus conventional assessment in critically ill patients postoperatively.

For the review of cost-effectiveness no studies were identified and as a consequence the data from the review of effectiveness were organised into a series of balance sheets.

## Summary of benefits

### *During surgery*

Five studies (453 patients) compared ODM plus CVP monitoring plus conventional assessment with CVP monitoring plus conventional assessment during surgery. There were fewer deaths [Peto odds ratio (OR) 0.13, 95% CI 0.02–0.96], fewer major complications (Peto OR 0.12, 95% CI 0.04–0.31), fewer total complications (fixed-effects OR 0.43, 95% CI 0.26–0.71) and shorter length of stay (pooled estimate not presented, 95% CI –2.21 to –0.57) in the ODM group. These analyses included a study of patients undergoing cardiac surgery, the results of which were consistent with those from the other four studies. The results of the meta-analysis of mortality should be treated with caution owing to the low number of events and low overall number of patients in the combined totals.

One study (61 patients) compared ODM plus conventional assessment with CVP monitoring plus conventional assessment during surgery. Confidence intervals for differences in mortality, total complications and length of hospital stay were wide enough to include clinically important differences favouring either intervention.

Three studies (139 patients) compared ODM plus conventional assessment with conventional assessment during surgery. There was no evidence of a difference in mortality (fixed-effects OR 0.81, 95% CI 0.23–2.77). No data were available on major complications. One study reported total complications, with fewer in the ODM group (OR 0.23, 95% CI 0.07–0.72) but no fewer patients experiencing complications (OR 0.41, 95% CI 0.14–1.16). Length of hospital stay was shorter in all three studies in the ODM group.

### *Critically ill patients*

Two studies (366 patients) compared ODM plus CVP monitoring plus conventional assessment versus CVP monitoring plus conventional assessment. The patient groups were quite different (cardiac surgery and major trauma) and neither

study, nor a meta-analysis, showed a statistically significant difference in mortality (fixed-effects OR 0.84, 95% CI 0.41–1.70). No data were available for major complications but fewer patients in the ODM group experienced complications (OR 0.49, 95% CI 0.30–0.81) and both studies reported a statistically significant shorter median length of hospital stay in the ODM group.

No evidence was available on quality of life and five studies reported the outcome of ODM-related complications, with all stating that none occurred.

## Costs

No studies reporting costs were identified. The addition of ODM would incur the cost of a monitor (approximately £10,000) which will last several years and typically a single disposable probe per patient (approximately £60–£120). In addition, maintenance contracts might be necessary (approximately £550). Apart from the few minutes required to insert the probe there are few other additional costs. Any changes in length of stay, complications and mortality would also affect total costs.

## Cost-effectiveness

No economic evaluations that met inclusion criteria were identified from the existing literature and a series of balance sheets were constructed to highlight the choices and trade-offs that may exist. For ODM plus CVP monitoring plus conventional assessment versus CVP monitoring plus conventional assessment during surgery, the ODM strategy is likely to be more effective and the costs of ODM are likely to be offset by reductions in length of stay and complications. However, the cost of interventions prompted by monitoring (intravenous fluids and vasoactive drugs, etc.) is not known. For ODM plus conventional assessment versus conventional assessment during surgery, it is likely that the costs of ODM will be offset by the reductions in length of stay, but the overall differences in costs and effectiveness are unclear as there is insufficient evidence on mortality and complications. For ODM plus conventional assessment versus CVP monitoring plus conventional assessment during surgery, there is insufficient evidence available and where data are available the confidence intervals are sufficiently wide to cover clinically and economically important differences favouring either intervention. In critically ill patients the cost of ODM appeared to be compensated for by differences in length of stay and its use may reduce complications, but the effect on mortality and on the cost of interventions prompted by monitoring is unclear.

A partial economic modelling exercise was conducted for ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment and ODM plus conventional clinical assessment versus conventional clinical assessment for high-risk surgical patients, as well as for ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment comparison for critically ill hospitalised patients. Results show that ODM strategies are likely to be considered cost-effective. More specifically, the threshold value for the extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective was estimated. The required magnitude of these costs ranged from £581 to £11,600. However, these results are heavily dependent on the underlying assumptions of the analyses (e.g. pairwise comparisons rather than comparisons of all relevant methods of monitoring, limited number of studies, limited or non-existent data on relevant outcomes, small sample sizes and different underlying conditions).

## Recommendations for research

Although some modest data are available and consideration can be given to the balance of costs and benefits using the data from the balance sheets, more formal economic evaluation would be desirable to make better use of the data available and to make valuations implicit in any decision more explicit. Furthermore, well-designed, multicentre RCTs are required among high-risk surgical patients to address the following question: Does ODM-guided fluid therapy plus conventional clinical assessment improve outcome with and without CVP monitoring compared with conventional clinical assessment with and without CVP monitoring?

All the identified studies were conducted in unconscious patients. Newer ODM probes that may be tolerated by awake patients are now manufactured and further research is needed to evaluate these.

Further research is required to assess the benefits of ODM-guided fluid administration during surgery and continuing into the early postoperative period versus the benefits of ODM-guided fluid administration during surgery alone. Further research is also required to determine the optimal number of hours for ODM-guided fluid administration to continue after surgery once the patient has been admitted to a critical care facility.

Given the paucity of the existing economic evidence base any further primary research should include an economic evaluation or should provide data suitable for use in an economic model.

# Chapter 1
# Background

## Description of health problem

Optimal management of cardiac output, fluid balance and haemodynamic status has long been considered key to improving outcome in critically ill patients and in high-risk patients undergoing major surgery. Traditionally, pulmonary artery catheters (PACs) have been used to monitor cardiac output and haemodynamic status to guide treatment. A recent Health Technology Assessment (HTA) Programme-funded study demonstrated that PAC insertion and management of critically ill patients using the variables monitored by PACs fails to confer an outcome benefit.[1] Further studies have also cast doubt on the value of PACs in high-risk major surgery.[2] This, coupled with concerns related to procedural complications associated with the insertion and use of the PAC, along with the development of less invasive cardiac output monitors in clinical practice, has resulted in a global decline in the usage of the PAC in recent years.

Less invasive technologies to monitor cardiac output and other haemodynamic variables include oesophageal Doppler monitoring (ODM), transoesophageal echocardiography, transthoracic impedance, carbon dioxide elimination and systems based upon pulse contour analysis and dye dilution methods.

Oesophageal Doppler monitoring measures blood flow velocity in the descending thoracic aorta using a flexible probe inserted into the patient's oesophagus with an ultrasound transducer at its tip. The information is combined with an estimate of aortic cross-sectional area (derived from a nomogram based on the patient's age, height and weight) and an estimate of the fraction of the cardiac output perfusing the upper body, allowing continuous monitoring of cardiac output and haemodynamic status. ODM is a relatively simple procedure requiring no calibration and minimal training and has a good safety profile. The probe itself is uncomfortable and often poorly tolerated by awake patients, therefore patients monitored with ODM generally need to be adequately sedated or anaesthetised. While this is often undertaken in patients requiring such monitoring, it does tend to limit the use of the probes to an operating theatre, high dependency unit (HDU) or intensive care unit (ICU) environment. Newer, softer probes designed to be tolerated in awake patients have been developed, but at present are not widely available.

Although described as continuously monitoring, the ODM probes often need to be refocused prior to each measurement, so they are normally used to make frequent, repeated measurements rather than to provide a beat-by-beat measure of stroke volume.

Transoesophageal echocardiography allows direct assessment of the heart's structure and function. It can also be used to derive cardiac output by measuring the Doppler shift in the reflected ultrasound beam to determine blood velocity and by direct measurement of the cross-sectional area of the aorta. It has several limitations as a technique: the probe is large and expensive; patients require considerable amounts of sedation or an anaesthetic to tolerate it; and a highly-skilled, highly-trained operator is required to operate the probe, as without one continuous monitoring of cardiac function is impossible.

Pulse contour analysis devices employ algorithms to calculate cardiac output from analysis of the arterial pressure/time waveform, and so require the presence of an indwelling arterial catheter (often present anyway in the targeted populations). There are several types of device available, but all require initial calibration with another measure of cardiac output which may be by means of either a transpulmonary thermodilution or lithium dilution technique. Systems using thermodilution to calibrate also require the presence of a central venous catheter, with its associated hazards. While lithium dilution calibration does not require the presence of a central venous catheter, the lithium used to calibrate the system can interact with muscle relaxant drugs used in anaesthesia. Therefore, care needs to be taken regarding timing of calibration. Pulse contour devices, while requiring calibration and taking slightly longer to set up than ODM, do have the advantage that they can be tolerated by awake patients.

Proponents of the use of cardiac output monitoring to guide fluid replacement and pharmacological treatment suggest this allows optimisation of the patient's haemodynamic status, helping to maintain adequate tissue perfusion. This, in turn, prevents overt or occult organ damage which hinders the patient's recovery. Thus, monitoring has the potential to reduce mortality, complications, lengths of stay in critical care facilities and overall hospital stays, all of which could result in savings in health-care costs.

Approximately 3 million surgical operations are conducted in the UK annually, with an overall hospital mortality rate of 0.8–1.0%.[3] The National Confidential Enquiry into Patient Outcome and Deaths (NCEPOD) reports that there were over 20,000 deaths following surgery in England, Wales and Northern Ireland alone in 2003.[4] Therefore, any improvement in morbidity and mortality for these patient groups would markedly improve important patient outcomes for large groups of patients as well as significantly improving utilisation of health-care resources.

## Current service provision

In the NHS, variation in practice exists with regard to haemodynamic optimisation and patient monitoring during the perioperative period and in critical care environments. Inevitably, the lack of published national guidelines or frameworks in this area contributes to these differences. The only published statement from the National Institute for Health and Clinical Excellence (NICE) with regard to ODM to date has been as part of NICE's Interventional Procedures (IP) Programme, relating only to safety and efficacy.[5] ODM was not felt to fall within the IP Programme's remit as it is considered standard clinical practice with risks and benefits that are sufficiently well known.

Within the NHS the ODM that is most widely used is the CardioQ™ device (Deltex Medical, Chichester, UK). There are CardioQ monitors in around two-thirds of the 300 or so NHS hospitals that regularly undertake moderate or major surgery within the UK. The probes are single use, and several types exist which can be used to monitor for periods of from 6 hours to 10 days. Currently the CardioQ is used to monitor around 25,000 patients each year within the NHS. While it is difficult to state accurately the categories of patients in whom the ODM probes are being used, information from the manufacturer suggests that approximately one-third are used in intensive care, one-third intraoperatively (theatre only) and one-third throughout the perioperative period (although given the large number of potential patients their use overall remains infrequent).

Given the large number of operations carried out within the NHS each year (in excess of 2 million) and the relatively small number of cardiac output monitors, many patients receive what might be termed conventional clinical assessment. The recent Agency for Health Care Research and Quality (ARHQ) report[6] defined this as follows:

> Conventional clinical assessment usually refers to non-invasive assessment of various clinical markers. In some institutions, fluid management may be based only on assessment of hemodynamic variables such as heart rate, systolic blood pressure and urinary output, with no measure of blood flow or CVP.

Such a definition would seem to be applicable to the NHS (although considerable variation in actual practice throughout the NHS might be expected).

## Description of technology under assessment

Oesophageal Doppler monitoring was first described by Side and Gosling in the early 1970s and since then there have been significant advances in the technology and its clinical use. ODM is currently used in a variety of clinical settings, most commonly in critical care environments and in patients undergoing surgery (particularly patients with significant co-morbidity or those undergoing major surgery with a high incidence of blood loss and/or significant fluid shifts.) ODM allows continuous monitoring of a patient's haemodynamic variables and, more importantly, allows the display of trends in these variables. This allows the clinician to titrate intravenous fluids and inotropic drugs to optimise tissue perfusion and oxygen delivery. The length of time this monitoring is required depends on the individual clinical situation. Upon completion of ODM the probe is simply removed.

The procedure measures blood velocity in the descending thoracic aorta using a flexible probe inserted into the patient's oesophagus via the mouth or nose. The tip of the probe contains a transducer which transmits an ultrasound beam. The tip is advanced to mid-thoracic level and

rotated to direct the ultrasound beam towards the descending aorta, allowing measurement of blood velocity using the Doppler frequency shift in the reflected ultrasound. This information is combined with an estimate of aortic cross-sectional area (derived from a nomogram based on the patient's age, height and weight) and upper body blood flow, allowing haemodynamic variables such as cardiac output, stroke volume and systolic flow time to be continuously measured. In addition, if other variables such as central venous pressure (CVP) and blood pressure are known, derived variables such as systemic vascular resistance can be calculated.

The probe and monitor are simple to use, and a period of training in groups of no more than 12 patients has been shown to be sufficient to ensure reliable measurements of cardiac output.[7] Generally speaking, the probe can be inserted and a clear signal can be obtained within a few minutes.

Oesophageal Doppler monitoring has been shown to have a high validity (no bias and high clinical agreement) for monitoring changes in cardiac output during the management of critically ill patients in both operating rooms and ICUs.[8] Good correlation also exists when comparing cardiac output measurements derived from ODM and PACs by means of thermodilution.[7,9–11]

Contraindications to insertion of ODM probes include patients under 16 years of age (special alternative probes and equipment are necessary for these patients), severe bleeding diathesis, facial trauma, oesophageal abnormalities such as varices, stents, strictures, carcinoma or oesophagitis and recent oesophageal or upper airway surgery. The presence of arrhythmias, severe aortic valve disease or a thoracic aortic aneurysm or the use of an intra-aortic balloon counterpulsation device, while not absolute contraindications to inserting the probe, may lead to difficulty in obtaining an accurate waveform and meaningful information.

Care needs to be taken in interpreting the data in certain other clinical situations as ODM makes the assumption that a constant proportion of the cardiac output enters the descending aorta, which is not always the case. Redistribution of blood flow between the ascending and descending aorta may occur during cross clamping of the aorta and with acute haemorrhage, where more of the cardiac output may be selectively diverted to coronary and cerebral circulation as opposed to the descending aorta. In addition, the presence of a sympathetic block to the lower body (such as that caused by epidural or spinal anaesthesia/analgesia) may lead to an overestimation of cardiac output.

Although there are no reported major complications resulting directly from the use of the ODM probe, a small number of minor complications have been reported in the literature, such as minor oral trauma and inadvertent tracheal placement of the probe.[6]

# Chapter 2
# The decision problem

As stated in Chapter 1, optimal management of cardiac output and haemodynamic status have long been considered key to improving outcome in critically ill patients and in high-risk patients undergoing major surgery. Currently, there are no universally accepted guidelines on how to select patients requiring cardiac output monitoring either perioperatively or in a critical care environment. Practice varies within the NHS because of a number of variables, notably individual clinician preferences, patient characteristics and local practices, guidelines or protocols.

## Aim and objectives of this review

Given this uncertainty about the role of cardiac output monitoring, the aim of this review was to assess the effectiveness and cost-effectiveness of one particular type of monitoring, ODM, when used for monitoring cardiac function in comparison with (a) standard care (i.e. no cardiac output monitor perioperatively) among critically ill patients and patients undergoing major surgery, and (b) other methods of monitoring heart function (such as PAC or pulse contour monitoring devices) in critically ill patients or in patients undergoing major surgery.

As described in subsequent chapters, the analysis focused on outcomes of most importance to patients (e.g. mortality, length of hospitalisation, length of stay in critical care and complication rates). Cost-effectiveness was assessed from the perspective of the NHS and personal social services.

In the following two sections, the place of cardiac output monitoring in the pathways of care of both patients undergoing major surgery and critically ill patients is briefly described.

## Use of cardiac output monitoring among patients undergoing major surgery

Cardiac output monitoring systems are used in operating theatres across all the major surgical specialties. They tend to be used predominantly for surgery of moderate to major severity, often in patients with significant co-morbidity or where significant blood loss or fluid shifts may be anticipated, as a consequence of either the patient's underlying condition or their anticipated surgery. However, not every patient undergoing major surgery will need to have their cardiac output monitored; generally they will be assessed preoperatively and the need for cardiac output monitoring will be determined by the anaesthetist based upon the clinical assessment, taking into account surgical factors and patient factors including co-morbidities (*Figures 1* and *2*). The anaesthetist may also be guided by the results of preoperative cardiac testing such as stress echocardiography or radionuclide cardiography (such tests are likely to be performed regardless of whether the use of ODM is an option).[12] Although the decision to use cardiac output monitoring is usually made preoperatively, occasionally factors encountered during surgery may lead to a decision to adopt monitoring during the intraoperative period, and this may continue into the postoperative period. Monitoring of surgical patients typically finishes at the end of the surgery.

## Use of cardiac output monitoring among critically ill patients

Patients requiring treatment in an ICU (level 3 care) or an HDU (level 2 care), by definition, need a higher level of care and monitoring than that available in general wards (level 1 care) (based on the Department of Health classification system). The decision to utilise these higher levels of care may be affected by a number of factors including patients' underlying surgical condition, their co-morbidities and the nature of surgery performed. In these complicated patients, haemodynamic function is frequently disturbed owing to a combination of the patient's existing disease(s) interacting with acute haemodynamic instability caused by surgery, anaesthesia, acute blood loss and fluid shifts. These complex interactions are not always apparent or easily interpretable using conventional clinical assessment and

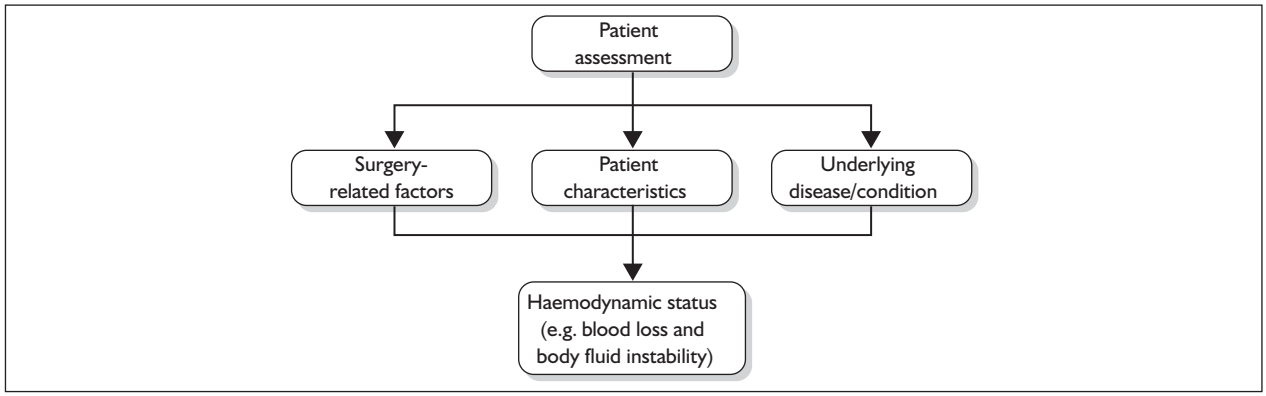


***FIGURE 1*** *Pre-surgery assessment of patient.*

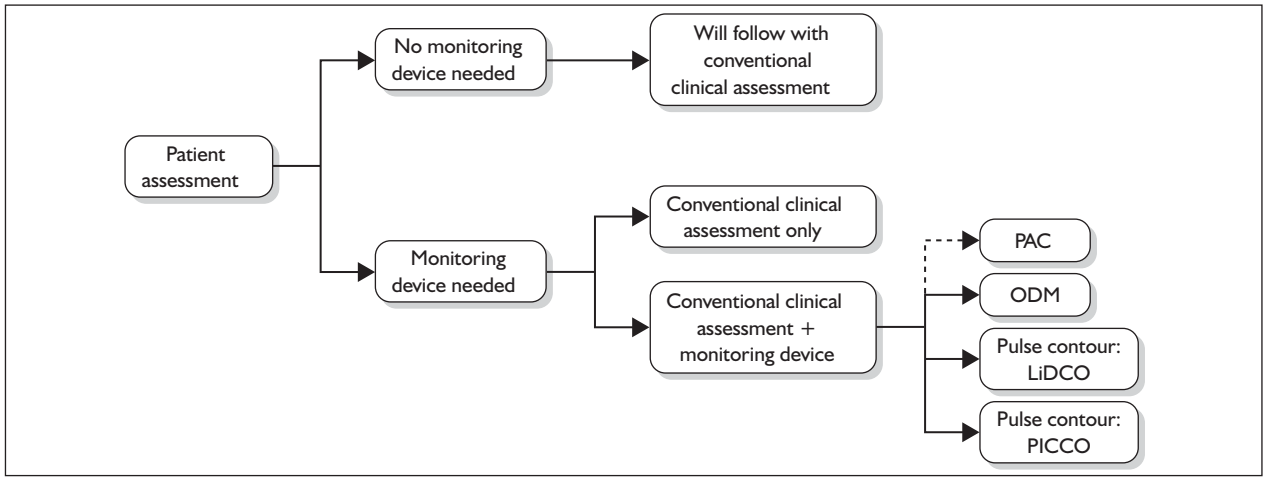


***FIGURE 2*** *Decision regarding use of cardiac output monitoring system.*

monitoring alone. In such patients, in addition to helping to guide and monitor operative fluid therapy, haemodynamic monitoring may also assist in differentiating between varying aetiologies of haemodynamic instability including hypovolaemia, sepsis and cardiogenic causes of tissue hypoperfusion or shock. This is important as the treatment for each of these pathologies is different. Among critically ill patients, monitoring would typically continue until there is a resolution of cardiovascular instability, which will be based on a broader clinical assessment.

# Chapter 3
# Effectiveness

In March 2007, a report conducted by the Emergency Care Research Institute (ECRI) Evidence-based Practice Center and commissioned by the US Agency for Healthcare Research and Quality (AHRQ) on behalf of the Centers for Medicare & Medicaid Services was identified. This report included a systematic review of ODM in patients during and/or after surgery, and reported patient-based outcomes that were similar to those included in the protocol for this review prepared by the Aberdeen Technology Assessment Review (TAR) group (see Appendix 1). Following discussion with the National Co-ordinating Centre for Health Technology Assessment (NCCHTA) it was agreed that the Aberdeen TAR group should base its review on the evidence contained in the AHRQ report, should it be judged to be of sufficiently high quality, supplemented by evidence from any additional studies identified.

The AHRQ report addressed the following four key questions:

1. What types of devices/techniques are currently used to assess cardiac output?
2. Does therapeutic management based on ODM during surgery lead to improved patient outcomes (fewer complications and shorter hospital stay)?
3. Does therapeutic management based on ODM during hospitalisation (defined hereafter as the use of ODM among critically ill patients) lead to improved patient outcomes (fewer complications and shorter hospital stay)?
4. What complications, harms and adverse events associated with ODM have been reported?

The comparators for key questions 2 and 3 were:

- PAC-based measurement of cardiac output using thermodilution
- Catheter-based measurement of CVP
- Conventional clinical assessment (physical examination, fluid input and output measurements).

This review focuses on the evidence presented in the AHRQ report, key questions 2 and 3. Definitions of the interventions are as described in the AHRQ report.[6]

The AHRQ report was critically appraised using the Database of Abstracts of Reviews of Effectiveness (DARE) criteria (see Appendix 2 for the appraisal of the AHRQ report, including details of inclusion and exclusion criteria, search strategy, data extraction and quality assessment strategy, methods, results and conclusions).

## Methods for reviewing effectiveness (Aberdeen TAR group)

### Search strategy

The search strategy involved the searching of electronic databases and relevant websites, contact with experts in the field and the scrutiny of bibliographies of retrieved papers. Extensive electronic searches were conducted to identify reports of published and ongoing studies on the clinical effectiveness of ODM. Searches were carried out for full text papers reporting on RCTs. The databases searched, from 1990 onwards, were: MEDLINE (1990–May week 3 2007), MEDLINE In-Process (23 May 2007), EMBASE (1990– 2007 week 20), CINAHL (1990–May week 2 2007), Science Citation Index (1990–20 May 2007), BIOSIS (1990–17 May 2007) and Cochrane Controlled Trials Register (Cochrane Library, Issue 2 2007) as well as current research registers [National Research Register (Issue 2 2007), Current Controlled Trials (May 2007) and Clinical Trials (May 2007)]. Additional databases searched for systematic reviews and other background information included the Cochrane Database of Systematic Reviews (Cochrane Library, Issue 2 2007), DARE (May 2007) and the HTA Database (May 2007). Websites of both professional organisations (including Anaesthesia UK, Critical Care, Intensive Care Society, International Collaboration for Excellence in Critical Care Medicine) and manufacturers (Deltex Medical, Arrow International) were also searched. Full details of the search strategies used and websites consulted are documented in Appendix 3.

## Inclusion and exclusion criteria

### *Types of study*

The types of study considered were randomised controlled trials (RCTs) and systematic reviews of such evidence.

The following types of study were excluded:

- non-randomised studies
- studies in which ODM was used as a measure of study outcome rather than as a monitoring tool leading to a clinical intervention
- non-English language studies
- animal models
- pre-clinical and biological studies
- narrative reviews, editorials and opinions
- reports published as meeting abstracts only.

### *Types of intervention*

The intervention considered was ODM.

### *Types of comparator*

Comparator interventions considered were:

- no cardiac output monitoring
- pulmonary artery catheters
- pulse contour analysis cardiac output monitoring
- lithium dilution cardiac output monitors, i.e. LiDCO™ monitor (LiDCO Group, London, UK)
- thermodilution cardiac output monitors, i.e. PiCCO® monitor (PULSION Medical Systems, Munich, Germany).

### *Types of participant*

The types of participant considered comprised:

- adults during major surgery
- adults managed in critical care facilities who required cardiac output monitoring.

The following subgroup analysis was considered in the event that sufficient evidence was available: patients with sepsis compared with those without sepsis.

### *Types of outcome*

The following patient-related outcomes were considered:

- mortality (30-day; hospital; longer-term)
- length of stay [critical care (ICU, HDU); hospital]
- days of organ support in the ICU
- postoperative complications and morbidity such as cardiac events and organ system failures
- quality of life in the year after surgery.

Length of hospital stay was defined as time from admission to discharge or death, and length of stay in critical care was defined as time from admission to critical care until discharge from critical care or death in a critical care facility.

## Data extraction strategy

One reviewer screened the titles (and abstracts if available) of all reports identified by the search strategy. Full text copies of all studies thought to be potentially relevant were obtained and one reviewer assessed them for inclusion. In the event of any uncertainty a second reviewer was consulted. Any disagreements were resolved by arbitration by a third party.

Data were extracted by one reviewer. Information was recorded on: year of publication; source of funding; study design; methods pre-randomisation (e.g. stratification); method of randomisation; concealment of allocation; blinding procedures; number and characteristics of participants; duration of interventions; choice of outcome measures; and length of follow-up. Reviewers were not blinded to authors, institutions or publications. Where there was deemed to be insufficient information in the published report, the authors were not contacted owing to the time constraints involved.

## Quality assessment strategy

The methodological quality of RCTs included in the review was to be assessed using the Delphi criteria list, adapted from Verhagen and colleagues.[13] However, in order to be consistent with the approach taken by the AHRQ report, the methodological quality of the two additional studies that were identified was appraised using the ECRI 25-question quality scale (see Appendix 4). ECRI used these 25 items to compute a summary score ranging from 0 to 10, with 10 indicating an ideal study and 0 indicating a study of the poorest quality. Individual item answers were converted to numerical scores by allocating 1 for each 'Yes' answer, −1 for each 'No' answer and −0.5 for each item that was not reported. The numerical scores for all 25 items were then added, 25 was added to the total, and this number was then divided by 50 and then multiplied by 10. These calculations

resulted in the 0–10 summary scale. Studies that scored $< 5$ were considered unacceptable quality, $> 5$ but $\leq 6.7$ were considered low quality, $> 6.7$ but $\leq 8.4$ were considered moderate quality, and $\geq 8.5$ were considered high quality.[6]

The methodological quality of the AHRQ report (key questions 2 and 3) was assessed using a previously validated 10-item checklist developed by Oxman and Guyatt (see Appendix 5).[14,15] This checklist contained nine criteria, checked as 'Yes', 'Partially' or 'No' depending on the extent to which they had been met. There was also one summary criterion for overall scientific quality, scored on a scale of 1–7, with 1 indicating 'extensive flaws' and 7 indicating 'minimal flaws'.

## Data analysis

For trials with multiple publications, only the most up-to-date or complete data for each outcome were included. Where appropriate, meta-analysis was employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses. It was originally planned to combine dichotomous outcome data using the Mantel–Haenszel relative risk (RR) method. However, to be consistent with the approach taken by the AHRQ report, dichotomous data were combined instead using odds ratios (ORs). When trials had roughly equal numbers of participants in each group and events were rare the Peto OR method was used. Continuous outcomes were combined using the inverse variance weighted mean difference (WMD) method. For the estimates of RR and WMD, 95% CIs and $p$-values were calculated. The results were reported using a fixed-effects model. Chi-squared tests and $I^2$ statistics were used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity were explored using sensitivity analysis. Where there was no clear reason for heterogeneity, the implications were explored using random effects methods. All meta-analyses were undertaken using Review Manager (RevMan) software. Where a quantitative synthesis was considered to be inappropriate or not feasible, a narrative synthesis of results was provided. Where a lack of uniformity of the data was present in many studies, a qualitative review looking for consistency between studies was performed. This was supplemented, where appropriate, by investigation of the consistency in the direction of the results using the Sign test.[16]

# Results

## Number of studies identified

The results of the searches are summarised in *Table 1* and *Figure 3*. The numbers retrieved from the searches in CINAHL, Science Citation Index (SCI), BIOSIS and CENTRAL include only the additional reports found after excluding those identified from the MEDLINE/EMBASE multifile search. A total of 663 reports were identified, of which 42 were selected for full assessment. As well

***TABLE 1*** *Search results*

| Database | Number retrieved | Number selected for assessment |
|---|---|---|
| MEDLINE/EMBASE/MEDLINE In Process multifile search (after deduplication in Ovid) | 444 | 15 |
| CINAHL | 4 | 0 |
| SCI | 69 | 6 |
| BIOSIS | 74 | 2 |
| CENTRAL | 15 | 5 |
| National Research Register | 32 | 8 |
| Current Controlled Trials | 10 | 2 |
| Clinical Trials | 1 | 1 |
| DARE | 5 | 2 |
| HTA Database | 6 | 0 |
| Cochrane Database of Systematic Reviews | 3 | 1 |
| Total retrieved | 663 | 42 |

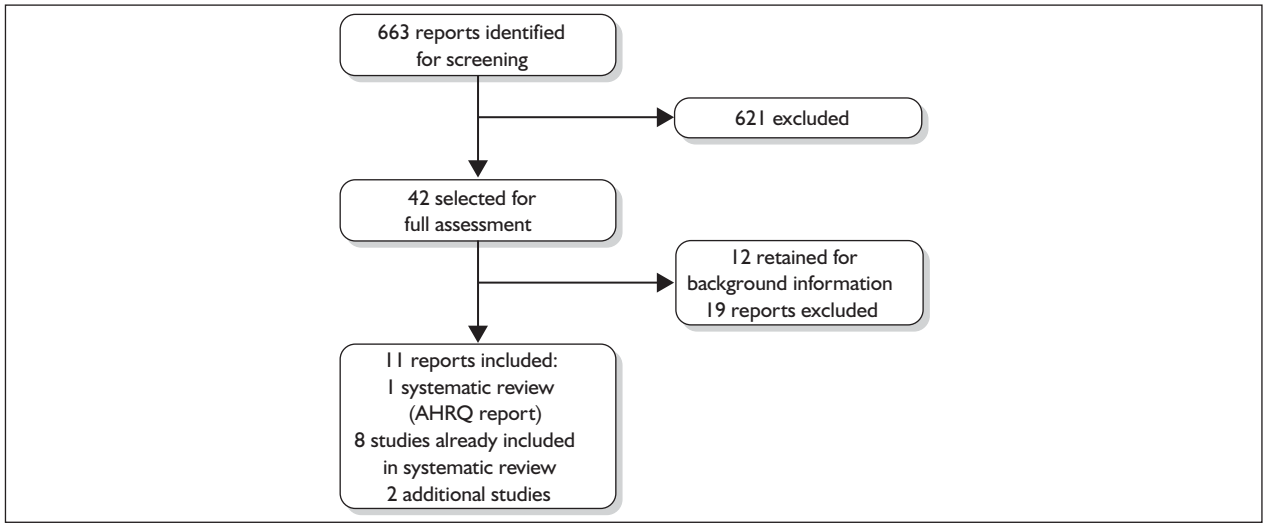


***FIGURE 3*** *Flow diagram outlining the screening process.*

as the AHRQ review,[6] 10 reports met inclusion criteria; eight of which had already been identified in the AHRQ review.

## Number and type of included studies

The AHRQ report[6] included eight RCTs.[17–24] Two additional RCTs were identified.[25,26]

## Number and type of excluded studies

A list of potentially relevant studies identified by the search strategy, for which full text papers were obtained but which subsequently failed to meet the inclusion criteria, is given in Appendix 6. These studies were excluded because they failed to meet one or more of the inclusion criteria in terms of types of study, participant, intervention or outcome.

## Characteristics of the included studies

The characteristics of the included studies are summarised in *Table 2* and the algorithms used to determine clinical responses are summarised in Appendix 7.

### *AHRQ report*

Eight RCTs[17–24] involving 757 patients were included that assessed the use of ODM either during surgery or among critically ill patients and reported patient-based outcomes. Seven studies[17,18,20–24] assessed ODM during surgery. The types of surgery performed included elective bowel surgery,[17,21,24] hip fracture repair surgery,[22,23] or elective general, urological or gynaecological surgery.[18] One study considered the use of ODM during elective cardiac surgery,[20] which might be considered separate from the other types of surgery. A further study by McKendry and colleagues[19] considered the use of ODM following surgery and compared ODM plus CVP monitoring plus conventional assessment with CVP monitoring plus conventional assessment in 174 patients admitted to cardiac intensive care following cardiac surgery.

Seven studies used the CardioQ ODM system (Deltex Medical Ltd, UK) or an earlier model while Conway and colleagues[17] used the TECO™ system (Medicina Ltd, UK), although the latter is no longer commercially available.

### *Additional studies*

Appendix 8 summarises the characteristics and results of the two additional studies that were identified. Dodd and colleagues[26] assessed the use of ODM (CardioQ) during surgery, comparing ODM plus conventional assessment with conventional assessment in 40 patients undergoing colorectal surgery. Chytra and colleagues[25] assessed the use of ODM (HemoSonic™ 100, Arrow International Inc., USA) in 162 multiple-trauma patients with major blood loss and compared ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment in these patients.

***TABLE 2*** *Characteristics of the included studies*[a]

| | AHRQ report | Additional studies | Total |
|---|---|---|---|
| Number of studies | 8 | 2 | 10 |
| Number of patients | 757 | 202 | 959 |
| Age [years (range of means/medians)] | ODM group: 56–82; control group: 59–85 | ODM group: 33–76; control group: 40–76 | ODM: 33–82; control: 40–85 |
| Sex | Male: 258 (52%); female: 234 (48%); NR: 265 | Male: 163 (81%); female: 39 (19%); NR: 0 | Male: 421 (61%); female: 273 (39%); NR: 265 |
| System used | CardioQ (7 studies); TECO (1 study) | CardioQ (1 study); HemoSonic 100 (1 study) | CardioQ: 8 studies; TECO: 1 study; HemoSonic 100: 1 study |
| ***Comparisons*** | | | |
| During surgery | ODM + CVP + conventional assessment vs CVP + conventional assessment (5 studies; 453 patients) | | 5 studies; 453 patients |
| | ODM + conventional assessment vs CVP + conventional assessment (1 study; 61 patients) | | 1 study; 61 patients |
| | ODM + conventional assessment vs conventional assessment (2 studies; 99 patients) | ODM + conventional assessment vs conventional assessment (1 study; 40 patients) | 3 studies; 139 patients |
| In critically ill patients | ODM + CVP + conventional assessment vs CVP + conventional assessment (1 study; 174 patients) | ODM + CVP + conventional assessment vs CVP + conventional assessment (1 study; 162 patients) | 2 studies; 336 patients |
| Type of surgery | Elective bowel surgery (3 studies; 293 patients) | | 3 studies; 293 patients |
| | Hip fracture repair surgery (2 studies; 130 patients) | | 2 studies; 130 patients |
| | Elective cardiac surgery (1 study; 60 patients) | | 1 study; 60 patients |
| | Elective general, urological or gynaecological surgery (1 study; 100 patients) | | 1 study; 100 patients |
| | | Colorectal surgery (1 study; 40 patients) | 1 study; 40 patients |

NR, not reported.
a The study by Venn and colleagues[23] reported two comparisons, and hence the ODM group appears twice. This study compared ODM plus conventional assessment ($n = 30$) vs CVP plus conventional assessment ($n = 31$) vs conventional assessment ($n = 29$).

## Quality of the included studies

*Table 3* summarises the quality assessment results for the studies included in the AHRQ report and for the two additional studies identified.

### *AHRQ report*

For ODM during surgery, the five studies comparing ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment had a median quality score of 8.9 (range 8.1–9.7) on the ECRI quality scale. This equates to a quality rating of 'high'. The two studies comparing ODM plus conventional clinical assessment with conventional clinical assessment had a median quality score of 9.0 (range 8.9–9.0). This also equates to a quality rating of 'high'. One of these studies[23] also compared ODM plus conventional

***TABLE 3*** *Summary of quality assessment results for studies included in the AHRQ report and the two additional studies identified*[a]

| | | AHRQ report | | Additional studies | |
|---|---|---|---|---|---|
| | **Comparison** | **Number of studies** | **Median quality score (range)** | **Number of studies** | **Quality score** |
| ODM during surgery | ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment | 5 | 8.9 (8.1–9.7) | 0 | NA |
| | ODM + conventional clinical assessment vs CVP + conventional clinical assessment | 1 | 9.0 | 0 | NA |
| | ODM + conventional clinical assessment vs conventional clinical assessment | 2 | 9.0 (8.9–9.0) | 1 | 8.8 |
| ODM in critically ill patients | ODM + CVP + conventional assessment vs CVP + conventional assessment | 1 | 8.5 | 1 | 7.4 |

NA, not applicable.
a The study by Venn and colleagues[23] appears twice in the table as it compared ODM plus conventional clinical assessment vs CVP plus conventional clinical assessment vs conventional clinical assessment.

clinical assessment with CVP monitoring plus conventional clinical assessment. For ODM use postoperatively among patients cared for in a cardiac care unit, McKendry and colleagues[19] compared ODM plus CVP monitoring plus conventional assessment with CVP monitoring plus conventional assessment, and their study had a quality score of 8.5, again equating to a quality rating of 'high'.

In terms of the individual studies' ratings against each of the 25 questions on the ECRI quality scale, for 17 of the questions all eight studies were checked 'Yes'. *Table 4* shows the questions which were checked 'No' or not reported ('NR') and in which studies this occurred.

### *Additional studies*

For ODM during surgery, the study by Dodd and colleagues,[26] which compared ODM plus conventional clinical assessment with conventional clinical assessment, had a quality score of 8.8 on the ECRI quality scale – a quality rating of 'high'. For ODM use postoperatively, the study by Chytra and colleagues,[25] which compared ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment, had a quality score of 7.4 – a quality rating of 'moderate'. The ECRI quality scale with the results for the two additional studies and an explanation of how the summary scores were calculated and categorised is given in Appendix 4.

In terms of the individual studies' rating against each of the 25 questions on the ECRI quality scale, for 18 of the questions both studies were checked 'Yes'. *Table 4* shows the questions that were checked 'No' or 'Not reported' (NR) and in which studies this occurred.

## Methodological quality of the AHRQ report

The methodological quality of the AHRQ report was assessed using the Oxman and Guyatt checklist[14,15] (see Appendix 5). This checklist contained nine criteria, checked as 'Yes' (the optimal answer), 'Partially' or 'No' depending on the extent to which they had been met. Six of the nine items were checked 'Yes', including whether the search methods were stated, whether the inclusion criteria were reported, whether the criteria used for assessing the validity of the included studies were reported, whether the validity of the included studies was assessed using appropriate criteria, whether the methods used to combine the findings of the studies were reported, and whether the authors' conclusions supported the data and/or the analysis reported in the review (although recommendations for further research were not provided).

Three items were checked as having been partially met, including whether the search for evidence was reasonably comprehensive (non-English language

***TABLE 4*** *ECRI quality assessment scale – questions checked 'No' or 'NR'*

| | AHRQ included studies | | | | | | | | Additional studies | |
|---|---|---|---|---|---|---|---|---|---|---|
| **ECRI quality assessment questions checked 'No' or 'NR'** | **Conway 2002[17]** | **Gan 2002[18]** | **McKendry 2004[19]** | **Mythen 1995[20]** | **Noblett 2006[21]** | **Sinclair 1997[22]** | **Venn 2002[23]** | **Wakeling 2005[24]** | **Chytra 2007[25]** | **Dodd 2004[26]** |
| Did the study employ stochastic randomisation? | | | | No | | No | | NR | No | NR |
| Were the characteristics of the patients in different groups comparable? | No | | NR | | | | NR | | | |
| Were subjects blinded to treatment? | | | | | | | | | No | |
| Did the authors test and confirm that blinding of patients was maintained? | NR | NR | NR | NR | NR | NR | NR | NR | No | NR |
| Was the treating physician blinded to group assignment? | No | No | No | No | | No | No | No | No | |
| Were the outcome assessors blinded to group assignment? | No | | No | | | | | | No | |
| Was there concealment of allocation? | | | | | | | | | NR | NR |
| Was the same treatment given to all of the patients enrolled in the experimental group? | | No | | | | | | | | |
| Was the same treatment given to all of the patients enrolled in the control group? | | No | | | | | | | | |
| Was the funding for this study derived from a source that does not have a financial interest in its results? | | No | No | | | | | | NR | NR |

NR, not reported.

studies were excluded), whether bias was avoided in the selection of articles (the number of reviewers who screened full text articles for inclusion was not stated) and whether the findings of the relevant studies were combined appropriately relative to the primary question (the participants were not considered homogeneous across studies as they were undergoing different types of surgery, although all involved procedures anticipating a major loss of blood or significant fluid shifts requiring fluid replacement; it was not stated how unit of analysis errors would be handled).

The AHRQ report scored 5 (minor bias) on the 10th item, a summary criterion for overall scientific quality on a scale of 1 (extensive flaws) to 7 (minimal flaws).

## Assessment of effectiveness

### *ODM during surgery*

### ODM plus CVP plus conventional clinical assessment versus CVP plus conventional clinical assessment

The only data available for this comparison came from the AHRQ report, from five studies involving 453 patients. The type of surgery performed included elective bowel surgery,[17,21,24] elective cardiac surgery[20] and elective general, urological or gynaecological surgery.[18]

#### *Mortality*

All five studies reported that no deaths occurred during surgery in either the ODM or the control group. Three studies[17,20,21] reported one death each in the control group (1/28; 1/30; 1/52, respectively) within 30 days following surgery, and one study[24] reported one death in the control group (1/64) within 60 days following surgery. However, the AHRQ report stated that the between-group differences were not statistically significant.

*Figure 4* shows a meta-analysis (Peto method) undertaken by the Aberdeen group of the five studies reporting mortality. This shows that ODM was associated with statistically significantly fewer deaths compared with control (OR 0.13, 95% CI 0.02–0.96). In this analysis the study by Mythen and colleagues,[20] which investigated elective cardiac surgery patients, has also been included and, even though the study is small, it exhibits a similar trend to that observed in the other studies. The meta-analysis results should be interpreted with caution because of the low number of events and the overall low number of patients in the combined totals.

#### *Major complications*

Three of five studies reported major complications,[17,20,21] which were generally defined as life threatening or requiring intensive or high-dependency care. The type of complications reported included severe tachyarrhythmias[17] and chest infection, multiple organ failure, respiratory failure, cerebrovascular accident and paralytic ileus.[20] All three studies showed a statistically significant difference in major complications that favoured the ODM groups (all of the major

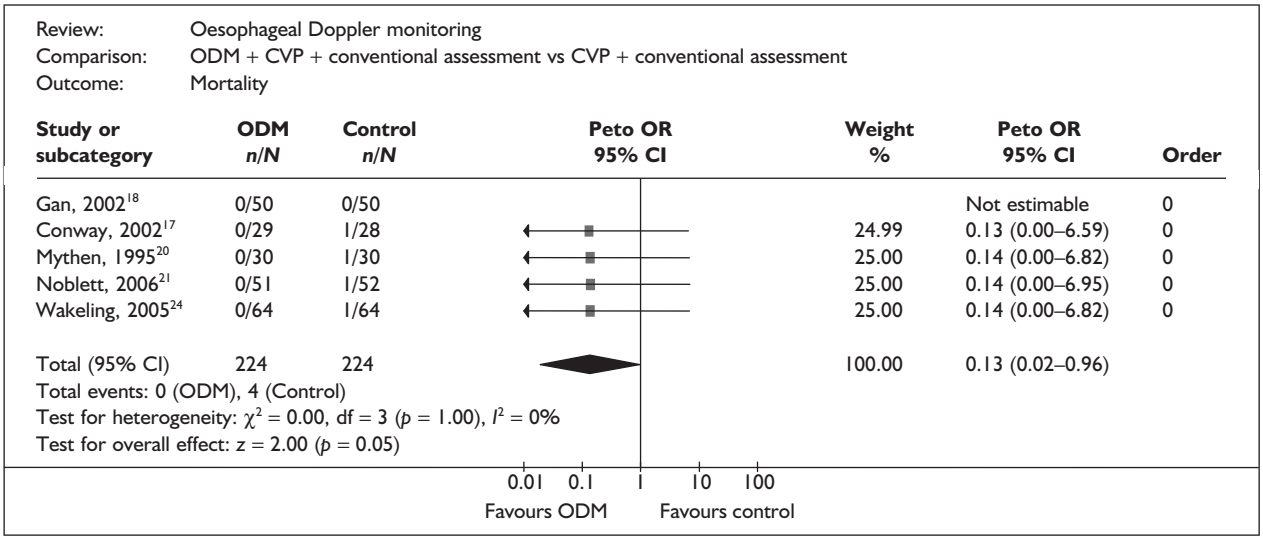


***FIGURE 4*** *Meta-analysis of studies reporting mortality (Aberdeen TAR group).*

complications occurred in the control groups). The AHRQ report stated that the ORs [Peto method; (95% CI)] for the three studies were −2.08 (−3.72 to −0.44),[21] −2.19 (−4.01 to −0.37)[17] and −2.19 (−3.86 to −0.51).[20] Although a meta-analysis was undertaken, the AHRQ report did not present a pooled estimate of effect size on the grounds that only three of the five studies (i.e. less than 80%) reported separate data on major complications. The 95% CI around the pooled estimate was 0.04–0.31, indicating that ODM was associated with statistically significantly fewer major complications.

*Figure 5* shows a meta-analysis (Peto method) undertaken by the Aberdeen group of the three studies reporting major complications, with the pooled estimate showing that ODM was associated with statistically significantly fewer major complications (OR 0.12, 95% CI 0.04–0.31). It is again worth noting that the data relating to use of ODM in cardiac surgery patients[20] are similar to those from the other studies reporting outcomes conducted on non-cardiac patients.

***Total complications***

Four studies reported total complications.[17,18,21,24] The AHRQ report stated that two studies showed a statistically significant difference, indicating fewer total complications in the ODM group (OR 0.23, 95% CI 0.10–0.54;[18] OR 0.41, 95% CI 0.20–0.84[24]). The other two studies also showed fewer complications in the ODM group, without reaching statistical significance (OR 0.44, 95% CI 0.13–1.54;[17] OR 0.47, 95% CI 0.20–1.07[21]). Gan and colleagues[18] reported the total number of complications rather than the number of patients with complications. Although a random-effects meta-analysis was undertaken, the AHRQ report did not present a pooled estimate of effect on the grounds that the studies reported complications somewhat differently (patients versus events). The 95% CI around the pooled estimate was −1.43 to −0.57, indicating that ODM was associated with statistically significantly fewer total complications.

*Figure 6* shows a meta-analysis undertaken by the Aberdeen group of the three studies that reported the number of patients in each group who experienced complications. The pooled estimate shows that ODM was associated with statistically significantly fewer total complications (OR 0.43, 95% CI 0.26–0.71).

***Length of hospital stay***

All five studies reported this outcome. The AHRQ report stated that four studies reported a statistically significant reduction in length of stay (based on either medians or means) associated with ODM, with a median of 6 versus 7 days, $p = 0.03$;[18] 7 (IQR 3–35) versus 9 (IQR 4–45) days, $p = 0.005$;[21] 10 (IQR 5.75) versus 11.5 (IQR 4.75) days, $p = 0.03$;[24] and a mean of 6.4 (range 5–9) versus 10.1 (range 5–48) days, $p = 0.01$.[20] The fifth study, by Conway and colleagues,[17] reported a median of 12 (range 7–103) days for the ODM group versus 11 (range 7–30) days for the control group ($p$-value not reported). *Table 5* shows the length of hospital stay for the five studies.

The AHRQ used a conservative method to impute effect sizes from the median, range and sample size when possible and conducted a random-effects

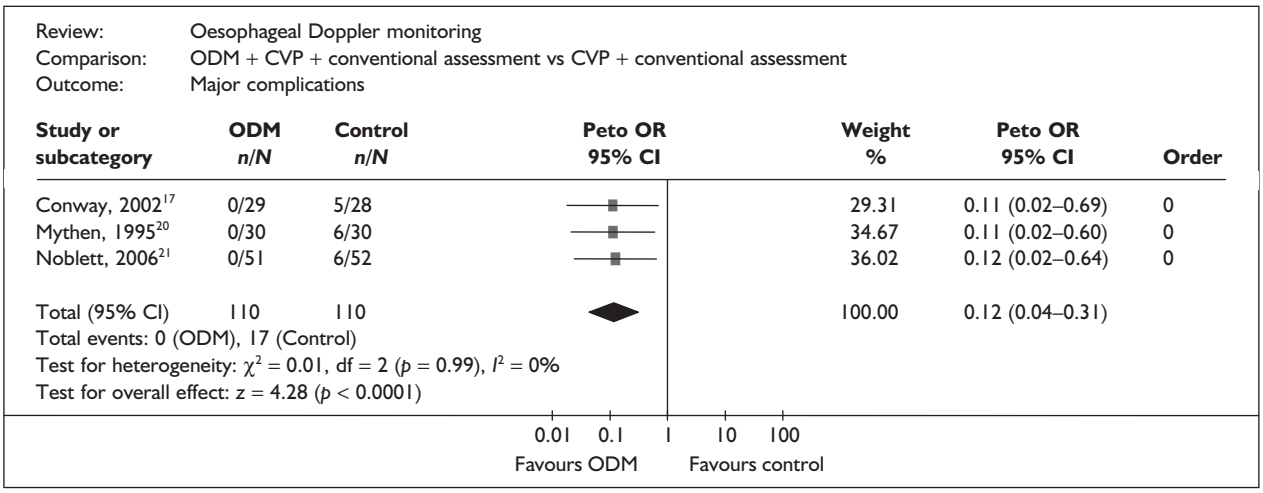


***FIGURE 5*** *Meta-analysis of studies reporting major complications (Aberdeen TAR group).*

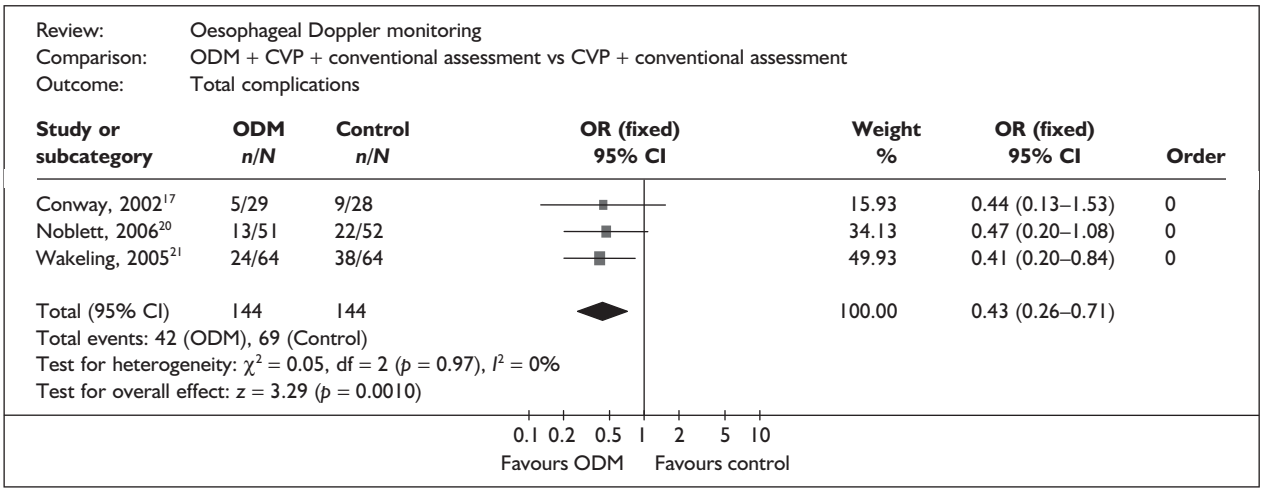


***FIGURE 6*** *Meta-analysis of studies reporting total number of patients with complications (Aberdeen TAR group).*

meta-analysis. An overall pooled estimate was not presented on the grounds that three of the five studies reporting this outcome did not present data that allowed a precise effect size to be calculated. However the 95% CI was presented; this was −2.21 to −0.57 days, indicating that ODM was associated with a statistically significantly shorter length of hospital stay.

Although the data should be treated extremely cautiously, *Figure 7* shows a meta-analysis undertaken by the Aberdeen group of the two studies reporting means and standard deviations for length of hospital stay. The pooled estimate shows that ODM was associated with a statistically significantly shorter length of hospital stay (WMD −1.82, 95% CI −2.98 to −0.65). There is evidence of heterogeneity which may be caused by differences between the two study population groups, although much of the difference in the mean length of stay in the Conway study was caused by one patient in the ODM group (see footnote, *Table 5*). As this meta-analysis includes only one of the four studies favouring ODM it might be argued that the estimate is slightly biased against ODM.

Overall, the data available for length of stay suggest that this may be shorter in the ODM group, although the precise magnitude of the difference is uncertain. However, the data from the Aberdeen meta-analysis also suggest that the type of patient may also be important.

***TABLE 5*** *Length of hospital stay (days)*

| Study | *n* | Measure | ODM group | Control group | *p*-value |
|---|---|---|---|---|---|
| [a]Conway 2002[17] | 57 | Mean (SD) | 18.7 (20.2) | 12.7 (6.0) | NR |
| | | Median (range) | 12 (7–103) | 11 (7–30) | NR |
| Gan 2002[18] | 100 | Mean (SD) | 5 (3) | 7 (3) | NR |
| | | Median | 6 | 7 | 0.03 |
| Mythen 1995[20] | 60 | Mean (range) | 6.4 (5–9) | 10.1 (5–48) | 0.01 |
| Noblett 2006[21] | 103 | Median (IQR) | 7 (3–35) | 9 (4–45) | 0.005 |
| Wakeling 2005[24] | 128 | Median (IQR) | 10 (5.75) | 11.5 (4.75) | 0.03 |

IQR, interquartile range; NR, not reported; SD, standard deviation.
a The report stated that in the study by Conway and colleagues[17] one patient in the ODM group remained in hospital for 103 days, not because of complications but because a social/community placement could not be found.
Source: AHRQ report.[6]

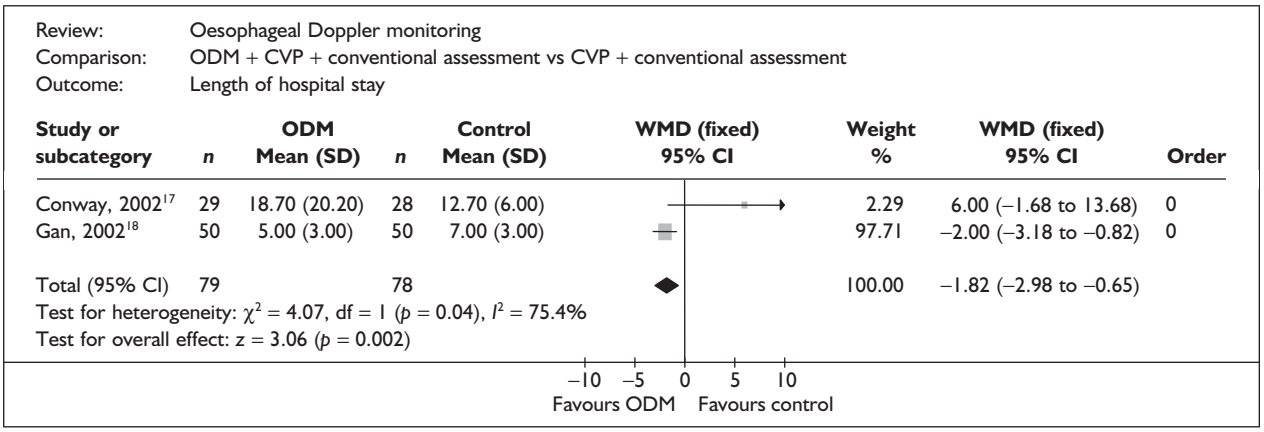


***FIGURE 7*** *Meta-analysis of length of hospital stay (Aberdeen TAR group).*

## ODM plus conventional clinical assessment versus CVP plus conventional clinical assessment

Again, the only data for this comparison came from the AHRQ report.[6] One study, by Venn and colleagues,[23] compared ODM plus conventional assessment ($n = 30$) with CVP monitoring plus conventional assessment ($n = 31$) in patients undergoing surgery for hip fracture repair (this study also included conventional assessment alone ($n = 29$) as a comparator, see below).

### *Mortality*

The AHRQ report stated that although there were fewer deaths in the ODM group (3/30) compared with the control group (6/31), the difference was not statistically significant ($p = 0.30$).

### *Major complications*

Venn and colleagues[23] did not report major complications separately from total complications.

### *Total complications*

There were 46.7% (14/30) complications in the ODM plus conventional assessment group compared with 51.6% (16/31) in the CVP monitoring plus conventional assessment group. The AHRQ report[6] stated that the difference in the rate of total complications (comprising mostly infections and cardiovascular events) favoured the ODM group without being statistically significant (OR 0.82, 95% CI 0.30–2.25). In terms of the number of patients experiencing complications, 33.3% (10/30) patients in the ODM group experienced complications compared with 45.2% (14/31) patients in the CVP monitoring group, again favouring the ODM group but without reaching statistical significance (OR 0.61, 95% CI 0.21–1.72).

### *Length of hospital stay*

The AHRQ report[6] stated that the difference in the mean length of hospital stay between the ODM and CVP monitoring groups was not statistically significant (13.5 versus 13.3 days, respectively, $p = 0.96$).

## ODM plus conventional clinical assessment versus conventional clinical assessment

The AHRQ report[6] included two studies that reported this comparison, involving 99 patients undergoing surgery for hip fracture repair.[22,23] An additional study to those included by the AHRQ report was identified. This was a poster by Dodd and colleagues[26] involving 40 patients undergoing colorectal surgery.

### *Mortality*

The AHRQ report stated that both studies reported that no deaths occurred during surgery. Venn and colleagues[23] reported that three (3/30) deaths occurred in the ODM group and two (2/29) occurred in the control group within 30 days following surgery, while Sinclair and colleagues[22] reported that one (1/20) death occurred in the control group during this period. Sinclair and colleagues[22] reported a further two deaths [one (1/20) in the ODM group and one in the control group] after this period and within 3 months following surgery. In terms of total mortality rates, the AHRQ report stated that neither study showed a statistically significant difference between the two treatment groups.

The additional study by Dodd and colleagues[26] reported hospital mortality of one (1/20) death in the ODM group and two (2/20) deaths in the control group.

*Figure 8* shows a meta-analysis of studies reporting mortality undertaken by the Aberdeen group, including the additional study by Dodd and colleagues,[26] with the pooled estimate failing to reach statistical significance and with confidence intervals sufficiently wide to include clinically important differences favouring either intervention (OR 0.81, 95% 0.23–2.77).

***Major complications***

Sinclair and colleagues[22] did not report complications and Venn and colleagues[23] did not report major complications separately from total complications. The additional study by Dodd and colleagues[26] did not report major complications.

***Total complications***

The AHRQ report stated that in the study by Venn and colleagues,[23] the ODM group experienced statistically significantly fewer complications (46.7%, 14/30) than the control group (79.3%, 23/29) (OR 0.23, 95% CI 0.07–0.72). However, in terms of the number of patients experiencing complications, the difference between the ODM group (33.3%, 10/30) and the control group (55.2%, 16/29) was not statistically significant and the confidence interval was sufficiently wide to contain clinically important differences favouring either intervention (OR 0.41, 95% CI 0.14–1.16).

The additional study by Dodd and colleagues[26] did not report total complications.

***Length of hospital stay***

The AHRQ report stated that both studies reported a shorter length of stay for the ODM group. Sinclair and colleagues[22] reported a statistically significantly shorter length of stay for the ODM group compared with the control group, with a median of 11 (range 3–23) days versus 20 (range 5–220) days, $p < 0.05$. In the study by Venn and colleagues,[23] although the ODM group experienced a shorter length of stay (mean 13.5 days, 95% CI 10.9–17.5) compared with the control group (mean 17.5 days, 95% CI 13.9–24.4) the difference was not statistically significant ($p = 0.31$). *Table 6* shows the length of hospital stay. In a random-effects meta-analysis undertaken by the AHRQ report, the pooled mean difference was statistically significant in favour of patients receiving ODM (mean difference −6.76, 95% CI −11.83 to −1.68).

The additional study by Dodd and colleagues[26] reported a shorter median (range) length of stay of 8 (5–34) days for the ODM group compared with 9 (5– 27) days for the control group, in terms of the number of days until medically fit for discharge. However, Dodd and colleagues[26] reported a longer median length of stay in the HDU of 3 (2–10) days for the ODM group ($n = 7$) compared with 2 (2–10) days for the control group ($n = 5$).

***ODM among critically ill patients***

**ODM plus CVP plus conventional clinical assessment versus CVP plus conventional clinical assessment**

The AHRQ report included one study[19] that reported this comparison in 174 patients admitted to cardiac intensive care following cardiac surgery, with the intervention group allocated to a fluid replacement algorithm guided by ODM during the first 4 hours after admission to cardiac intensive care. An additional study by Chytra and colleagues[25] was identified, involving 162 multiple-

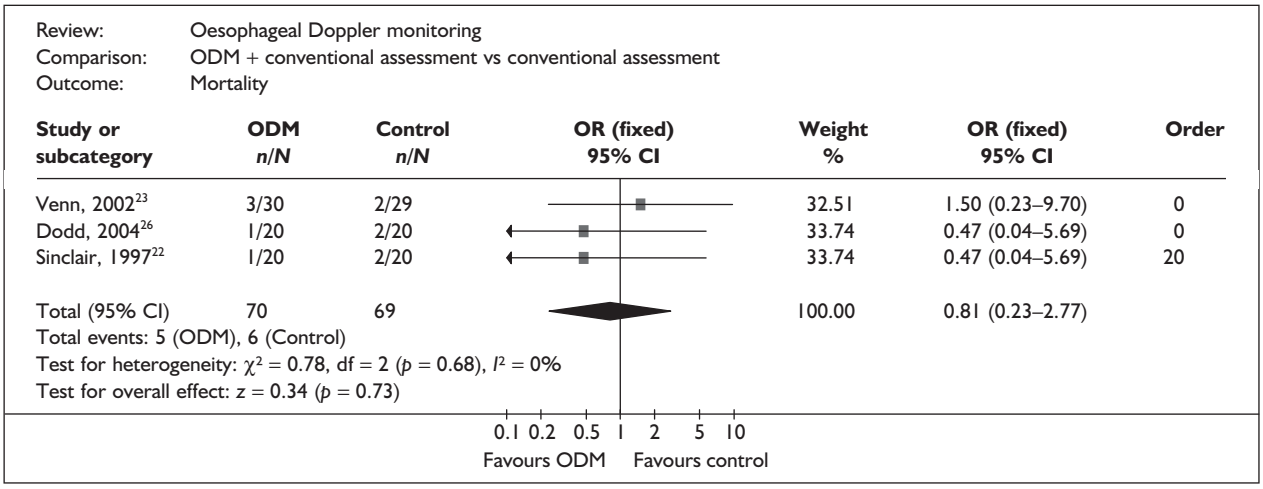


***FIGURE 8*** *Meta-analysis of studies reporting mortality (Aberdeen TAR group).*

***TABLE 6*** *Length of hospital stay (days)*

| Study | *n* | Measure | ODM group | Control group | *p*-value |
|---|---|---|---|---|---|
| [a]Dodd 2004[26] | 40 | Median (range) | 8 (5–34) | 9 (5–27) | NR |
| Sinclair 1997[22] | 40 | Median (range) | 11 (3–23) | 20 (5–220) | < 0.05 |
| Venn 2002[23] | 90 | Mean (95% CI) | 13.5 (10.9–17.5) | 17.5 (13.9–24.4) | 0.31 |

NR, not reported.
a Data are for number of days until medically fit for discharge.

trauma patients admitted to an ICU following surgery, with the intervention group allocated to a fluid replacement algorithm guided by ODM during the first 12 hours after admission to the ICU.

### *Mortality*

The AHRQ report stated that in the study by McKendry and colleagues[19] there were more deaths in the ODM group (4/89) compared with the control group (2/85) although the difference was not statistically significant ($p = 0.43$). Chytra and colleagues[25] reported fewer deaths in the ODM group (13/80) compared with the control group (18/82). Although the groups of patients included in the two studies might be considered very different, a meta-analysis was undertaken by the Aberdeen group of the studies reporting mortality (*Figure 9*). The OR for each study individually was not statistically significant, with the confidence intervals being sufficiently wide to include clinically important differences favouring either intervention. The pooled estimate also failed to reach statistical significance (OR 0.84, 95% CI 0.41–1.70). The results of the meta-analysis should be interpreted with caution owing to the very different types of patient included in the two studies.

### *Major complications*

Although McKendry and colleagues[19] stated that there was a trend towards fewer major postoperative complications and deaths in the ODM group, major complications were not reported separately from total complications. The additional study by Chytra and colleagues[25] also did not report major complications separately.

### *Total complications*

The AHRQ report stated that although fewer patients in the ODM group (19.1%, 17/89) experienced complications compared with the control group (30.6%, 26/85), the difference was not statistically significant ($p = 0.08$). In the additional study by Chytra and colleagues,[25] fewer patients in the ODM group (18.8%, 15/80) experienced infectious complications compared with the control group (34.1%, 28/82), with the difference being statistically significant ($p = 0.032$). *Figure 10* shows a meta-analysis undertaken by the Aberdeen group of the studies reporting the number of patients with complications, with ODM

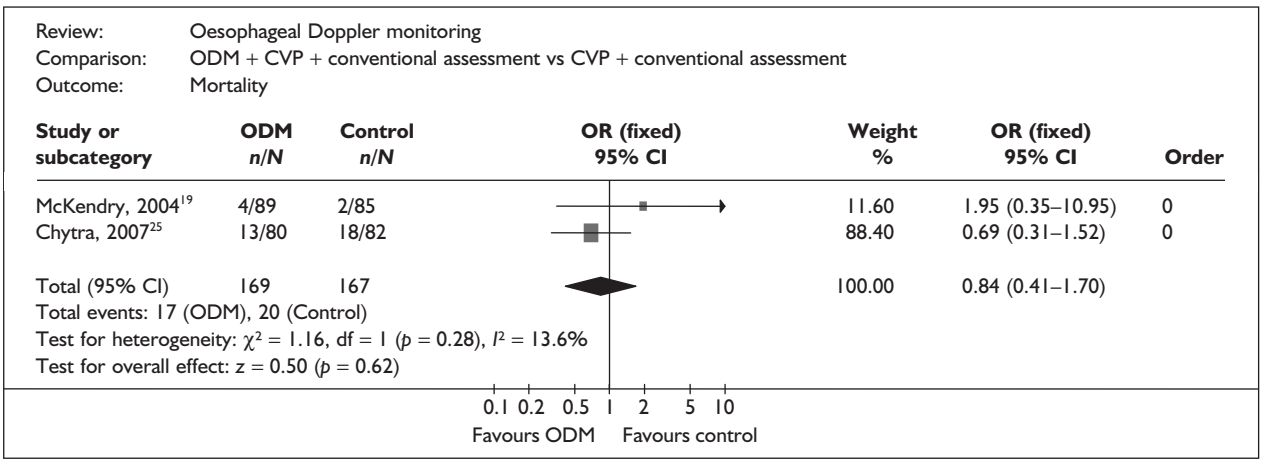


***FIGURE 9*** *Meta-analysis of studies reporting mortality (Aberdeen TAR group).*

being associated with statistically significantly fewer complications (OR 0.49, 95% CI 0.30–0.81). Again caution must be exercised when interpreting this meta-analysis as the patient groups in the two studies were different.

***Length of hospital stay***

The AHRQ report[6] stated that there was a statistically significantly shorter median length of stay in the ODM group (7 days, range not reported) compared with the control group (9 days, range not reported), $p = 0.02$. The mean length of stay was also shorter in the ODM group (11.4 days) compared with the control group (13.9 days), $p$-value not reported. In the additional study by Chytra and colleagues[25] there was a statistically significantly shorter median length of stay in the ODM group (14 days, IQR 8.25–21) compared with the control group (17.5 days, IQR 11–29), $p = 0.045$. *Table 7* shows the length of hospital stay.

Chytra and colleagues[25] also reported a statistically significantly shorter ICU median length of stay in the ODM group (7 days, IQR 6–11) compared with the control group (8.5 days, IQR 6–16), $p = 0.031$.

## Summary

The evidence on ODM presented in this chapter is based on the AHRQ report,[6] supplemented by two additional studies that were identified.[25,26] The eight RCTs[17–24] included in the AHRQ report and the two additional RCTs[25,26] reported the use of ODM in patients during surgery or among critically ill patients. The four outcomes reported by the AHRQ report were mortality, major complications, total complications and length of hospital stay.

None of the studies reported quality of life data. None of the studies reported results for patients with sepsis compared with those without sepsis.

The AHRQ report used an ECRI 25-question scale to assess the quality of the included studies. This scale was also applied to the additional studies that were identified. In the AHRQ report, for all comparisons reported by more than one study, the median quality score fell within the range ≥8.5 to 10.0, a quality rating of 'high' for this evidence base. The additional study by Dodd and colleagues[26] also received a quality rating of 'high', while the study by Chytra and colleagues[25] fell within the range > 6.7 but ≤8.4 and received a quality rating of 'moderate'.

The AHRQ report scored 5 (minor bias) on a scale of 1 (extensive flaws) to 7 (minimal flaws) on the Oxman and Guyatt checklist[14,15] for assessing the methodological quality of systematic reviews.

Five studies involving 453 patients reported ODM plus CVP monitoring plus conventional assessment versus CVP monitoring plus conventional assessment during surgery.[17,18,20,21,24] The AHRQ report did not pool mortality data. In meta-analyses undertaken by the Aberdeen group, pooled estimates showed statistically significantly fewer deaths in the ODM group (Peto OR 0.13, 95% CI 0.02–0.96) and a statistically significant reduction in the incidence of major complications (Peto OR 0.12, 95% CI 0.04–0.31) and total complications (fixed-effects OR 0.43, 95% CI 0.26–0.71). However, as noted above, as the number of deaths was low and the total combined sample size was modest, the pooled estimate for mortality should be interpreted with caution. In four of five

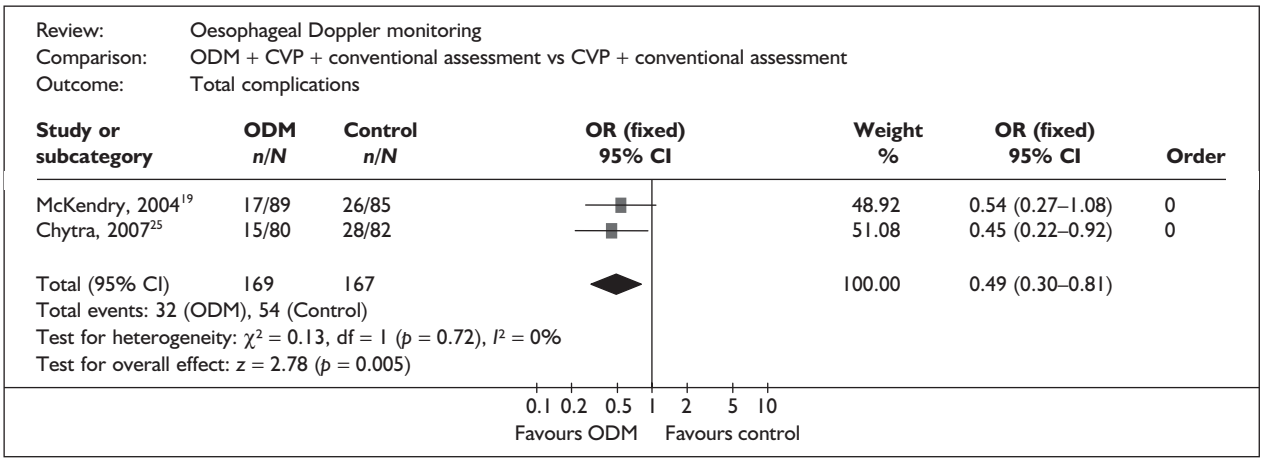


***FIGURE 10*** *Meta-analysis of studies reporting total number of patients with complications (Aberdeen TAR group).*

***TABLE 7*** *Length of hospital stay (days)*

| Study | *n* | Measure | ODM group | Control group | *p*-value |
|---|---|---|---|---|---|
| Chytra 2007[25] | 162 | Median (IQR) | 14 (8.25–21) | 17.5 (11–29) | 0.045 |
| McKendry 2004[19] | 174 | Mean | 11.4 | 13.9 | NR |
| | | Median | 7 | 9 | 0.02 |

IQR, interquartile range; NR, not reported.

studies reporting length of hospital stay, there was a statistically significant difference in favour of ODM, with a median of 6 versus 7 days, $p = 0.03$,[18] 7 (IQR 3–35) versus 9 (IQR 4–45) days, $p = 0.005$,[21] 10 (IQR 5.75) versus 11.5 (IQR 4.75) days, $p = 0.03$,[24] and a mean of 6.4 (range 5–9) versus 10.1 (range 5–48) days, $p = 0.01$.[20] A random-effects meta-analysis undertaken by the AHRQ report showed a statistically significantly shorter length of hospital stay in favour of the ODM group (pooled estimate not presented, 95% CI −2.21 to −0.57). One of the studies included in this comparison considered the use of ODM among elective cardiac surgery patients.[20] This group of patients might be considered to be different from patients undergoing other forms of surgery. Nevertheless, the results from this study were consistent with the results of the others.

Only Venn and colleagues[23] reported ODM plus conventional assessment versus CVP monitoring plus conventional assessment during surgery, in a study involving 61 patients. Although the outcomes reported favoured the ODM group, none were statistically significant and confidence intervals were sufficiently wide to include clinically important differences favouring either treatment.

Two studies[22,23] included in the AHRQ report and one additional study[26] involving a total of 139 patients reported ODM plus conventional assessment versus conventional assessment during surgery. None of the studies showed a statistically significant difference in mortality, and in a meta-analysis of the three studies undertaken by the Aberdeen group, the pooled estimate was not statistically significant (fixed-effects OR 0.81, 95% CI 0.23–2.77). None of the studies reported the outcome of major complications. Only Venn and colleagues[23] reported total complications, with the AHRQ report stating that there was a statistically significant difference in favour of the ODM group in terms of the number of complications (OR 0.23, 95% CI 0.07–0.72) but not in terms of the number of patients experiencing complications (0.41, 95% CI 0.14–1.16).

One study[19] included in the AHRQ report and one additional study[25] involving a total of 336 patients reported ODM plus CVP monitoring plus conventional assessment versus CVP monitoring plus conventional assessment among critically ill patients. Neither study showed a statistically significant difference in mortality, and in a meta-analysis undertaken by the Aberdeen group, the pooled estimate was not statistically significant (fixed-effects OR 0.84, 95% CI 0.41–1.70). There may be some concerns that the patient groups included in the two studies were very different, so this pooled estimate should be treated with caution. Neither study reported the outcome of major complications. In a meta-analysis undertaken by the Aberdeen group of total complications, the two studies showed a similar trend and the pooled estimate showed that statistically significantly fewer patients in the ODM group experienced this outcome (OR 0.49, 95% CI 0.30–0.81). In terms of length of hospital stay, the AHRQ report[6] stated that in the study by McKendry and colleagues[19] there was a statistically significantly shorter median length of stay in the ODM group compared with the control group (7 versus 9 days, $p = 0.02$), and the study by Chytra and colleagues[25] also reported a statistically significantly shorter median length of stay in favour of the ODM group compared with the control group (14 versus 17.5 days, $p = 0.045$).

In terms of ODM-related complications, five studies[17,21,22,23,25] reported that none occurred, while the remaining five[18,19,20,24,26] made no mention of ODM-related complications.

# Chapter 4

# Systematic review of economic evaluations

This chapter presents the results of a systematic review of economic evaluations of ODM compared with relevant comparators in the management of high-risk surgical patients and critically ill hospitalised patients. In order to better understand the choices and trade-offs between the various interventions, a simple balance sheet showing resource use and outcomes is also presented.

## Methods

### Search strategies

Studies that reported both costs and outcomes of ODM compared with the cardiovascular monitoring devices and conventional clinical care for the management of those undergoing major surgery and for critically ill patients, that met inclusion criteria, were sought from a systematic review of the literature. No language restrictions or limitations to searches were imposed.

Databases searched were MEDLINE (1990–June week 3 2007), EMBASE (1990–week 26 2007), MEDLINE In-Process (29 June 2007), SCI (1990–1 July 2007), NHS Economic Evaluation Database (NHS EED) (May 2007), HTA Database (May 2007) and Health Management Information Consortium (HMIC) (1990–May 2007). Other sources of information consulted included references in relevant articles and selected experts in the field. Websites of both professional organisations (including Anaesthesia UK, Critical Care, Intensive Care Society, International Collaboration for Excellence in Critical Care Medicine) and manufacturers (Deltex Medical, Arrow International) were also searched. Full details of the search strategies used are documented in Appendix 3.

### Inclusion and exclusion criteria

In order to be included, studies had to compare, in terms of both costs and outcomes, strategies involving ODM compared with no cardiac monitoring, PAC or pulse contour analysis monitoring for the monitoring of critically ill and high-risk surgical patients. Studies were included even if they made no formal attempt to relate cost to outcome data in a cost-effectiveness or cost–utility analysis. Two reviewers assessed all abstracts for relevance and full papers were obtained for those that appeared potentially relevant.

### Data extraction strategy

It was planned that the following data be extracted for each included primary study using the framework provided for abstracts prepared for the NHS EED:[27]

1. Study identification information
   i. author and year
   ii. interventions studied
   iii. type of economic evaluation
   iv. country of origin and currency reported
2. Intervention, study design and main outcomes
   i. fuller description of treatment
   ii. numbers receiving or randomised to each intervention
   iii. outcomes studied
3. Sources of data
   i. effectiveness data
   ii. mortality and co-morbidity (if measured)
   iii. cost data
   iv. quality of life (if measured)
4. Methods and study perspective
5. Results
   i. costs
   ii. benefits
   iii. incremental cost-effectiveness/utility ratio (ICER)
   iv. sensitivity analyses
6. Additional comments relating to the design and reporting of the economic evaluation. For reviews of economic evaluations, it was planned that data would be extracted on:
   i. the nature of the review methodology used
   ii. the inclusion criteria for studies
   iii. the number of studies identified
   iv. the method of quality assessment for individual economic evaluations
   v. the conclusions drawn on the relative efficiency of the alternative methods.

### Quality assessment strategy

One economist was to assess included studies using the NHS EED guidelines for reviewers.[27]

### Data synthesis

No data synthesis was performed.

## Results

### Number of studies identified

The results of the literature search are presented in *Table 8*. The number of reports retrieved from the search in SCI and HMIC is the total after deduplication against the results of the MEDLINE/EMBASE multifile search.

Eleven papers were selected from the searches, none of which met the inclusion criteria for the systematic review, and were selected for background information purposes only. Details of these studies can be obtained from the authors.

## Balance sheet

As described above, no economic evaluations that met the inclusion criteria were found from the systematic search of the literature. It was, therefore, not possible to provide any comment on the comparative costs and/or effects of ODM in comparison with relevant comparators. To give an idea of the impact that regular use of ODM might have on the NHS in terms of costs and effects, a series of balance sheets were drawn up. The balance sheet presents the differences between interventions, in terms of resource use and natural and clinical measures of effectiveness. Such an approach serves to highlight the choices and trade-offs between the various monitoring modalities.

Nonetheless, any decision based on the balance sheet approach is made using an implicit (rather than an explicit) synthesis of the available data.

### Comparisons made

Data gathered from the review of effectiveness reported in Chapter 3 compared various strategies involving ODM use for patients following major surgery and for hospitalised patients. In total, three different strategies involving ODM versus no ODM were extracted from the literature for high-risk surgical patients. Only one strategy involving ODM versus no ODM was extracted from the current literature in relation to critically ill hospitalised patients. No evidence was available for the comparison of strategies that include ODM compared with PAC and/or thermodilution techniques. Therefore, all comparisons relate to the use of conventional clinical assessment and/or the use of CVP monitoring. Separate balance sheets are presented for each strategy and patient group and, where possible, a pooled effect size from the meta-analysis conducted as part of the review of effectiveness is reported (*Tables 9, 10, 11* and *12*).

### Results of balance sheets

#### *High-risk surgical patients*

#### Comparison of ODM plus CVP plus conventional clinical assessment with CVP plus conventional clinical assessment

This comparison (*Table 9*) had the greatest number of studies contributing data to it and, as the pooled estimates demonstrate, the addition of ODM consistently outperforms the no ODM strategy. However, these results should be treated with caution as the number of studies contributing for each estimate as well as the sample sizes were small, and some of them were conducted in patient groups with different underlying conditions. In

***TABLE 8*** *Results of searching for studies on cost-effectiveness*

| Database | Hits screened | Selected for full assessment |
|---|---|---|
| MEDLINE/EMBASE/MEDLINE In-Process multifile search (after deduplication in Ovid) | 113 | 10 |
| SCI | 10 | 0 |
| HMIC | 0 | 0 |
| HTA Database | 6 | 1 |
| NHS EED | 23 | 0 |
| Total | 152 | 11 |

***TABLE 9*** *Balance sheet comparing ODM plus CVP plus conventional clinical assessment with CVP plus conventional clinical assessment for high-risk surgical patients*

| ODM + CVP + conventional clinical assessment | CVP + conventional clinical assessment |
|---|---|
| Reduction in mortality (OR 0.13, 95% CI 0.02–0.96) leading to increased patient benefits | Reduction in mortality following use of ODM leading to potential increased management costs of survivors in the longer term |
| Reduction in major complications (OR 0.12, 95% CI 0.04–0.31) leading to increased patient benefits and lower treatment costs | Additional costs of ODM: staff time, reusable and disposable equipment required for insertion, monitoring and removal of the probe |
| Reduction in total complications (OR 0.43, 95% CI 0.26–0.71) leading to increased patient benefits and lower treatment costs | |
| Reduction in length of hospital stay (WMD –1.82, 95% CI –2.98 to –0.65) acting as a proxy for earlier recovery and implying lower treatment costs | |
| ***No evidence of a difference in*** | |
| Cost of additional interventions, e.g. use of intravenous fluids or drugs prompted by the monitoring | |

terms of resource usage, it is known that in order to monitor cardiac output with ODM, an ODM monitor and probe are required as well as an anaesthetist to perform the insertion (a procedure of only a few minutes in duration). Further, based on clinical advice, it is known that this technology would be used predominantly in an HDU/ICU or the operating theatre setting (Drs Gordon Houston and Brian Cuthbertson, July 2007, personal communication). Data provided by manufacturer Deltex Medical indicate that the one-off cost of the CardioQ Doppler monitor is approximately £8000. The disposable probe ranges in price from £60 for a clinically clean probe lasting up to 6 hours to £121 for a sterile probe that lasts up to 10 days. Deltex Medical also states that the delivered cost of a probe is the only direct cost of using the probe other than a negligible amount per patient relating to the cost of ultrasound gel. It is possible that more than one probe may be required per patient. This decision will be influenced by the choice of the initial probe, which in turn depends upon a prior clinical judgement as to how a patient will respond. Several pricing schemes exist in relation to the acquirement of the monitor; e.g. a rental agreement for the monitor is a common method whereby a monitor is placed in the hospital free of charge with a varying incremental cost for every probe purchased (£0–£15), depending on the volume of probes purchased. With reference to the various pricing schemes, it should be stressed that significant variation between centres is common owing to the standard practice of direct individual negotiation with manufacturers in NHS centres.

Information from Deltex Medical also suggests that the reusable monitoring device is likely to last many years, although some costs in terms of maintenance and servicing would be incurred. A standard 1-year service contract might cost approximately £550. It might be reasonable to assume, however, that the additional cost per patient in terms of reusable equipment alone would be negligible, and that the main additional cost of ODM would be the cost of the disposable probes.

Although it should be treated cautiously as it is based on the synthesis of two small studies considering different patient groups, the pooled estimate of a 1.82 day reduction in hospital stay for ODM patients (*Table 9*) would result in a cost saving per patient in terms of length of stay only on an ICU ward of £3123 per patient, given the unit cost of £1716 for a day on a Level 3 ICU ward (the most frequently cited level of care).[28] Similarly, if the hospital days saved related to a stay on an HDU ward, the cost saving would be £1431, assuming a unit cost of £786 for a day on a Level 2 HDU ward (again the most frequently cited level).[28] Finally, if the reduction in length of stay is related to a stay on a general surgical ward, the cost saving for a 1.82 day reduction in length of stay would be £564.[29] While the precise cost of the staff time and equipment required for ODM monitoring has not been estimated it could be inferred that the cost per patient of the addition of ODM is likely, at the very least, to be less than the cost savings associated with the reduction in length of stay for ICU and HDU patients. The use of monitoring may also

lead to some forms of treatment being initiated (e.g. the use of intravenous fluids, etc.). Arguably, the ODM group may receive more interventions and/or more appropriate interventions. However, the net effect on cost is uncertain.

**Comparison of ODM plus CVP plus conventional clinical assessment with CVP plus conventional clinical assessment**

For this comparison, again, it is known that there would be additional costs associated with the use of ODM, i.e. equipment and staffing, although there is no evidence of a difference in the main selected measures of outcome (*Table 10*). As fewer studies contributed data to this comparison it is not as clear what cost savings in terms of length of stay, for example, might be found.

**Comparison of ODM plus conventional clinical assessment with conventional clinical assessment for high-risk surgical patients**

*Table 11* shows the balance sheet for this comparison. As any difference in length of stay might be considerable (OR −6.76, 95% CI −11.83 to −1.68), if such a difference exists it is highly likely that savings in length of stay would more than compensate for the cost of using ODM. However, it is less clear from the evidence available whether total costs will indeed be less as there are insufficient data available to identify differences in mortality, complications or the costs of treatments incurred because of monitoring, and the confidence intervals surrounding such estimates are sufficiently wide to include clinically and economically important differences. Similarly, there is insufficient evidence to judge whether the use of ODM increases total benefits. Therefore, should ODM be adopted, a judgement would have to be made that the trends in favour observed for other comparisons would be maintained for this comparison.

***Critically ill hospitalised patients***

For this group of patients data were available for one comparison: ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment. The balance sheet for this comparison is shown in *Table 12*. It appears there are likely to be reductions in total complications and length of hospital stay though the evidence relating to this particular subgroup of patients is sparse. What we cannot directly tell from the balance sheet is the likely impact on cost. As noted above the effect on cost of additional interventions prompted by the monitoring is unclear. It is also unclear what savings may accrue through reductions in length of stay (reported as 1–2 days for this comparison). Given the unit cost for a day on an ICU ward of £1716, an HDU ward cost of £786 and general medical ward cost of £310 then the cost of using ODM may reasonably be expected to be compensated for by this reduction in length of stay.[28,29] However given the uncertainty surrounding the effect on mortality and major complications then a decision to adopt ODM would imply that a judgement has been made that the reduction in mortality and complications observed for other uses of ODM would be continued in this setting.

***TABLE 10*** *Balance sheet comparing ODM plus conventional clinical assessment with CVP plus conventional clinical assessment for high-risk surgical patients*

| ODM + conventional clinical assessment | CVP + conventional clinical assessment |
|---|---|
| Additional costs of CVP: staff time, reusable and disposable equipment required for insertion, monitoring and removing of catheter | Additional costs of ODM: staff time, reusable and disposable equipment required for insertion, monitoring and removal of the probe |
| ***No evidence of a difference in*** | |
| Mortality | |
| Major complications | |
| Total complications | |
| Length of hospital stay | |
| Cost of additional interventions, e.g. use of intravenous fluids or drugs prompted by the monitoring | |

***TABLE 11*** *Balance sheet comparing ODM plus conventional clinical assessment with conventional clinical assessment for high-risk surgical patients*

| **ODM + conventional clinical assessment** | **Conventional clinical assessment** |
|---|---|
| Reduction in length of hospital stay (WMD –6.76, 95% CI –11.83 to –1.68) acting as a proxy for earlier recovery (provided mortality in the ODM group is no greater than conventional assessment) and implying lower treatment costs | Additional costs of ODM: staff time, reusable and disposable equipment required for insertion, monitoring and removal of the probe |
| ***No evidence of a difference in*** | |
| Mortality (OR 0.81, 95% CI 0.23–2.77). Unclear if there are any additional benefits to patients following use of ODM and if there are any additional costs for ODM for care in the longer term | |
| Major complications. Total complications per patient (OR 0.41, 95% CI 0.14–1.16). Unclear if there are any additional benefits to patients following use of ODM and if there are any savings for ODM following a reduction in total complications | |
| Cost of additional of interventions, e.g. use of intravenous fluids or drugs prompted by the monitoring | |

***TABLE 12*** *Balance sheet comparing ODM plus CVP plus conventional clinical assessment with CVP plus conventional clinical assessment for critically ill hospitalised patients*

| **ODM + CVP + conventional clinical assessment** | **CVP + conventional clinical assessment** |
|---|---|
| Reduction in total complications (OR 0.49, 95% CI 0.30–0.81) leading to increased patient benefits and lower treatment costs | Additional costs of ODM: staff time, reusable and disposable equipment required for insertion, monitoring and removal of the probe |
| Reduction in length of hospital stay (length of stay 1–2 days less) acting as a proxy for earlier recovery (provided mortality in the ODM group is no greater than conventional assessment) and implying lower treatment costs | |
| ***No evidence of a difference in*** | |
| Mortality (OR 0.84, 95% CI 0.41–1.70). Unclear if there are any additional benefits to patients following use of ODM and if there are any additional costs for ODM for care in the longer term | |
| Major complications. Unclear if there are any additional benefits to patients following use of ODM and if there are any savings for ODM following a reduction in major complications | |
| Cost of additional of interventions, e.g. use of intravenous fluids or drugs prompted by the monitoring | |

## Recent evidence on the cost-effectiveness of alternatives to ODM

Although no data were identified that were relevant to a comparison of ODM, a previous HTA monograph reported findings from a systematic review and RCT of the effectiveness and cost-effectiveness of PAC in patient management in intensive care.[1] Within the trial, 55 (10.9%) patients in the PAC group and 179 (35.2%) patients in the control group received transoesophageal Doppler monitoring. However, no separate results were presented for these patients. The HTA suggests that PAC was unlikely to be cost-effective for this group of patients. The HTA also provided an indication of the cost drivers, i.e. the major determinants of the differences in cost between the interventions compared. It is likely that the costs of ODM compared with the costs of no ODM will be driven by similar factors, primarily length of stay differences. The trial reported in the HTA found that for the financial year 2002–3, the cost per day in an ICU was £1353. Thus, if the addition of ODM to high-risk surgical and critically ill hospitalised patients does lead to a significant reduction in length of ICU stay, it is likely to have a large impact

on cost. Other things being equal, if the costs of equipment and staffing associated with ODM per patient were to be less than £310 [a conservative estimate based on data from Information Servicers Division (ISD) Scotland][29] regular ODM use is likely to be cost saving, especially if we take into account the cost information supplied by the manufacturer (Ewan Phillips, Deltex Medical, July 2007, personal communication).

## Summary

This chapter presents the overall evidence currently available on the cost-effectiveness of ODM compared with relevant comparators in the management of critically ill hospitalised patients and high-risk surgical patients, based on a systematic review of the literature. No economic evaluations that met inclusion criteria were identified and little extra knowledge of the cost-effectiveness of ODM relative to the various strategies could be ascertained.

In order to explore the choices and trade-offs of the various monitoring modalities, a balance sheet was presented for each strategy for which evidence was available from the review of effectiveness. Some evidence indicates that ODM might be expected to be more efficient than not using ODM but any judgement depends upon the strategies compared. Further information for the critically ill hospitalised patient group compared with high-risk surgical patients is required owing to the sparse data on this patient group. The trade-offs highlighted by the balance sheets could be further informed by more formal consideration of the balance of probabilities in terms of which strategy is or is not likely to be cost-effective.

In terms of effectiveness, it should be noted that no comparisons of ODM with thermodilution or PAC methods were found and that, therefore, such comparisons are not included in this review or on the balance sheet.

# Chapter 5
# Economic modelling

The balance sheets comparing resource use and outcomes for the different strategies considered in the systematic review of effectiveness presented in Chapter 4 give an idea of the different trade-offs faced by the decision-maker when choosing a particular strategy. However, unless all relevant factors favour one strategy then decisions based on these usually rely on implicit valuations of the trade-offs that may exist. These valuations may differ from person to person and might lead to different policy decisions being made that are difficult to debate objectively. One of the main assets that economic models have is their ability to make explicit many of these implicit weights. This chapter explores the scope for an economic model to assess the relative cost-effectiveness of using ODM.

## An economic model for ODM

Drummond and colleagues defined economic evaluation as the 'comparative analysis of alternative courses of action in terms of both their costs and consequences,' ideally over the remaining lifetime of the patient.[30] Economic evaluations are an important aid to decision-making because (a) a systematic analysis makes it easier to identify clearly the relevant alternatives; (b) such an approach makes explicit the viewpoint of the analysis; and (c) without some attempt at measurement, the uncertainty surrounding orders of magnitude can be critical.

Moreover, there are certain characteristics that an economic model should have in order to be a sound basis for decision-making. Among these is that it should include all the relevant alternatives for comparison and should allow for appropriate information to be taken into account within the evaluation. The model can be thought of as describing the pathways of care that a patient may follow in situations where ODM is and is not used. A potential model structure should consider strategies that include no cardiac monitoring, alone or in combination with technologies such as pulse contour analysis monitoring, lithium dilution cardiac monitors (i.e. LiDCO monitor), and thermodilution cardiac monitors (i.e. PiCCO monitor), as comparators for strategies that include ODM. A similar model structure could be outlined for the use of ODM within hospital critical care.

By clearly structuring the decision problem it is possible to highlight the data that are needed to fully inform any decision. However, it is possible that decisions might be reasonably made without all these data. In subsequent sections we explore how the data that are currently available can be used more fully to inform judgements on cost-effectiveness.

## Cost of ODM

In this section data provided by a manufacturer, Deltex Medical, as well as data from public sources have been used to estimate the extra (incremental) costs associated with ODM. *Table 13* shows the annual total cost of ODM assuming a 5-year lifetime for the monitor. The costs of ODM are based on data provided by Deltex Medical (Ewan Phillips, Deltex Medical, August 2007, personal communication).

The cost of the probes varies from £60 for a 6-hour oral/nasal Doppler probe for use intraoperatively or perioperatively to £121 for a 10-day sterilised oral Doppler probe for use in critical care. Information from the manufacturer indicated that the use of more than one probe by a patient was rare. Therefore, it was assumed that the number of probes used per monitor per year is similar to the number of patients receiving ODM per year. However, this will depend upon the initial selection of the probe and the prior clinical judgement as to how the patient will respond. Given the nature of the patient groups it might be expected that the use of more than one probe would be more common among critically ill than surgical patients.

It is unclear how many patients might use a monitor per year (i.e. how intensively the equipment is used) and what would be the optimal use rate in a potential steady state. For instance, the average length of stay in an ICU in Scotland's hospitals is 4.7 days[31] (for an HDU it is 3.2 days). This does not mean, however, that a particular monitor would be used, on average, every 5 days as this would imply a full-time usage assumption

***TABLE 13*** *Cost per year for ODM equipment (£) 2007–8*

| | Concept | CardioQ | CardioQP[a] |
|---|---|---|---|
| 1 | Cost of monitor | 8000 | 11,000 |
| 2 | Monitor lifetime (assumption) | 5 years | 5 years |
| 3 | Yearly instalments | 1600 | 2200 |
| 4 | Other yearly costs (maintenance and software) | 1200 | 1200 |
| 5 | Total yearly cost | 2800 | 3400 |

a CardioQ supports only adult probes while CardioQP supports both adult and paediatric probes.

for this equipment. Moreover, patients receiving critical care (within either an ICU or an HDU) who require ODM might not be representative of the whole population of patients receiving critical care, and their length of stay may be higher or lower than the average. Given the absence of data on the length of use of ODM, a simple assumption can be made about the number of patients who might be treated with a single monitor within a given year. For illustrative purposes, in this exercise three usage rates per monitor per year have been considered (36, 125 and 500) to explore the impact of different levels of intensity of use (*Table 14*). These figures result from an assumption of 250 days of usage of equipment per year and different numbers of patients treated (i.e. one patient every 7 days, one patient every 2 days and two patients per day, respectively).

*Table 15* shows estimations of the total cost for ODM equipment and probe per patient. Based on the assumptions stated above and according to the probe used the total equipment cost can range from around £66 to £214 per patient.

When estimating costs of a procedure it would be usual to include other categories of cost such as the staff time involved. However, the marginal staff cost of using ODM may be minimal as the staff required to interpret the outputs of the monitor will be there anyway. Furthermore, the time it takes to insert the probe and obtain the initial readings is also minimal (e.g. about 5 minutes; Dr Gordon Houston, July 2007, personal communication). Other direct costs associated with the procedure, such as ultrasound gel or other disposal materials, are negligible. As indicated in Chapter 4, one category of costs not included in these analyses is the cost of treatments incurred as a result of monitoring. The net effect and magnitude of these costs is uncertain.

## Further estimation of the implications for cost-effectiveness

This section explores the cost-effectiveness of ODM for the different comparisons presented in Chapters 3 and 4. The analyses focused on two outcomes: mortality and length of hospital stay. Worst- and best-case scenarios for the use of ODM were constructed for each comparison. These scenarios differed in terms of the cost of ODM equipment (e.g. £214 for worst-case and £66 for best-case scenario, as reported in *Table 15*), and the

***TABLE 14*** *ODM equipment cost per patient (£) 2007–8*

| Concept | CardioQ | CardioQP[a] |
|---|---|---|
| Monitor cost per year | 2800.00 | 3400.00 |
| ***Assumption*** | | |
| (a) 36 patients per monitor per year | 76.71 | 93.15 |
| (b) 125 patients per monitor per year | 22.40 | 27.20 |
| (c) 500 patients per monitor per year | 5.60 | 6.80 |

a CardioQ supports only adult probes while CardioQP supports both adult and paediatric probes.

***TABLE 15*** *Total equipment cost (equipment and probe) for ODM (£) 2007–8*

| Concept | CardioQ | CardioQP |
|---|---|---|
| ***Assumption***[a] | | |
| Using assumption (a) and £121 probe price | 197.71 | 214.15 |
| Using assumption (b) and £96 probe price | 118.40 | 123.20 |
| Using assumption (b) and £60 probe price | 82.40 | 87.20 |
| Using assumption (c) and £96 probe price | 101.60 | 123.20 |
| Using assumption (c) and £60 probe price | 65.60 | 66.80 |

a £121 for a 10-day sterilised oral Doppler probe (critical care); £96 for a 72-hour awake nasal Doppler probe (intra- and perioperative); £60 for a 6-hour oral/nasal Doppler probe (intra- and perioperative).

cost attached to any reduction in the length of stay due to ODM. For the worst-case scenario this was taken to be equal to £310 per day (corresponding to the cost of a day in a general medical ward) and for the best-case scenario the cost used was £1680 per day, which corresponds to the cost of a day in an ICU.[31] Finally, the mean length of survival per additional survivor was taken to be 1 year for the worst-case scenario and 5 years for the best-case scenario. These numbers help to illustrate the trade-offs that might be faced.

Results are presented in terms of QALYs. For these calculations a quality of life weight [as measured by the European Quality of Life-5 Dimensions (EQ-5D) scale] at 12 months of 0.66 was used. This estimate is based on quality of life of ICU survivors at 12 months (lower than the 0.88 score that might be estimated for the general population[32]).

Finally, in order to allow for the statistical imprecision surrounding estimates of the differences in mean length of stay and survival, normal and lognormal distributions, respectively, were used to describe the uncertainty in these parameters. The data required to construct these distributions were the estimated confidence intervals reported in Chapter 3 and, as such, the same limitations as stated in Chapters 3 and 4 apply to this economic evaluation exercise.

## High-risk surgical patients

### *ODM plus CVP plus conventional clinical assessment versus CVP plus conventional clinical assessment for high-risk surgical patients*

*Table 9* shows a balance sheet for the ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment comparison for high-risk surgical patients. In favour of ODM it shows reduction in mortality (OR 0.13, 95% CI 0.02–0.96), reduction in major complications (OR 0.12, 95% CI 0.04–0.31), reduction in total complications (OR 0.43, 95% CI 0.26–0.71) and reduction in length of hospital stay (WMD −1.82, 95% CI −2.98 to −0.65). Conversely, favouring the non-use of ODM there are the additional costs for ODM and potentially increased management costs for survivors due to a lower mortality rate in the ODM group. With the cost calculations obtained for ODM in the previous section and focusing on the reduction in mortality, it is possible to illustrate the extent of the increment in health-care costs and QALYs per additional survivor before ODM would not be considered cost-effective at a £30,000 per QALY threshold.[33]

*Figure 11* shows the results for ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment for high-risk surgical patients. The probabilistic sensitivity analysis was based on 1000 iterations of a Monte Carlo analysis. The black line represents the £30,000 cost per QALY threshold and the circles on the right and below this line are iterations of the model that indicate that the use of ODM would be cost-effective. The more circles there are to the right of and below the line the more likely it is that the use of ODM would be cost-effective. The white circle in the middle of the black circle 'cloud' is the incremental cost-effectiveness based on the point estimates for each of the parameters used in assessing cost-effectiveness.

It can be seen in *Figure 11* that a great majority of the points lie within the second quadrant; this indicates that using ODM together with CVP

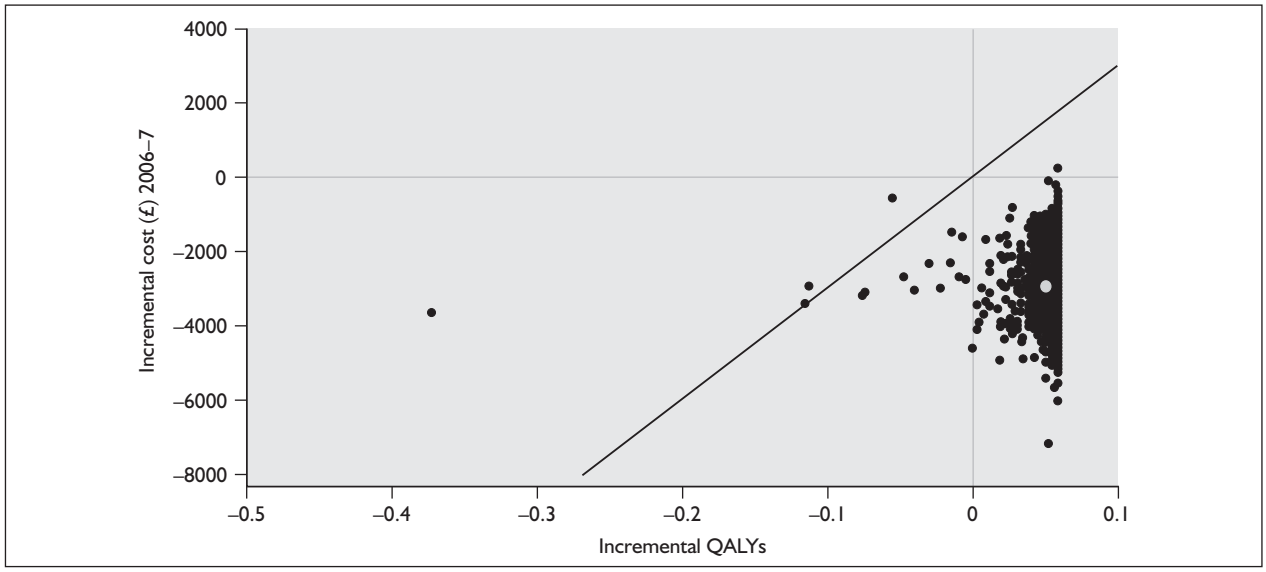


***FIGURE 11*** *Incremental cost-effectiveness plane – best-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

monitoring and conventional clinical assessment seems to be more effective and less costly than using only CVP monitoring and conventional clinical assessment. A similar result can be observed in *Figure 12* for the worst-case ODM scenario. Note that the cloud appears truncated on the right because of our assumption of a 1- or 5-year increment to length of life for additional survivors.

*Figures 13* and *14* show the average extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective. In terms of *Figures 11* and *12* this is equivalent to moving the circles upward and crossing the £30,000 threshold. For the best-case scenario this mean that the extra cost per additional survivor would be £4441 (95% CI £2151–£6732) and for the worst-case scenario the extra cost per additional survivor would be £642 (95% CI £225–£1060).

Caution should be taken when reading these results as calculations did not take into account the other issues favouring ODM (e.g. the reductions in complications that the calculations assume are fully captured by the reductions in length of stay and increases in survival). The incorporation of all these factors into a full economic model might give a better idea of the likelihood of ODM being cost-effective.

Further analysis was undertaken using data from the AHRQ report on the difference in length of hospital stay. These data are more conservative than those used above. A lognormal distribution was attached to these data using the 95% CI, i.e. −2.21 to −0.57 days. The other data used in this model are the same as those used for the worst-case model presented above.

The great majority of points from the probabilistic sensitivity analysis lie in the second quadrant, where using ODM together with CVP monitoring and conventional clinical assessment seems to be more effective and less costly than using only CVP monitoring and conventional clinical assessment (*Figure 15*). However, should the mean incremental cost per additional survivor be £448 or more (95% CI £117–£779) then the ODM-based strategy would no longer be considered cost-effective (*Figure 16*).

#### *ODM plus conventional clinical assessment versus CVP plus conventional clinical assessment for high-risk surgical patients*

Unfortunately, there are no feasible exercises for this comparison as there are no data on which calculations could be based. This means that it is not possible to provide any sensible estimates of the incremental costs and benefits of ODM for this clinical scenario.

#### *ODM plus conventional clinical assessment versus conventional clinical assessment for high-risk surgical patients*

*Table 11* shows the balance sheet for this comparison. In favour of ODM a reduction in length of hospital stay (OR −6.76, 95% CI −11.83

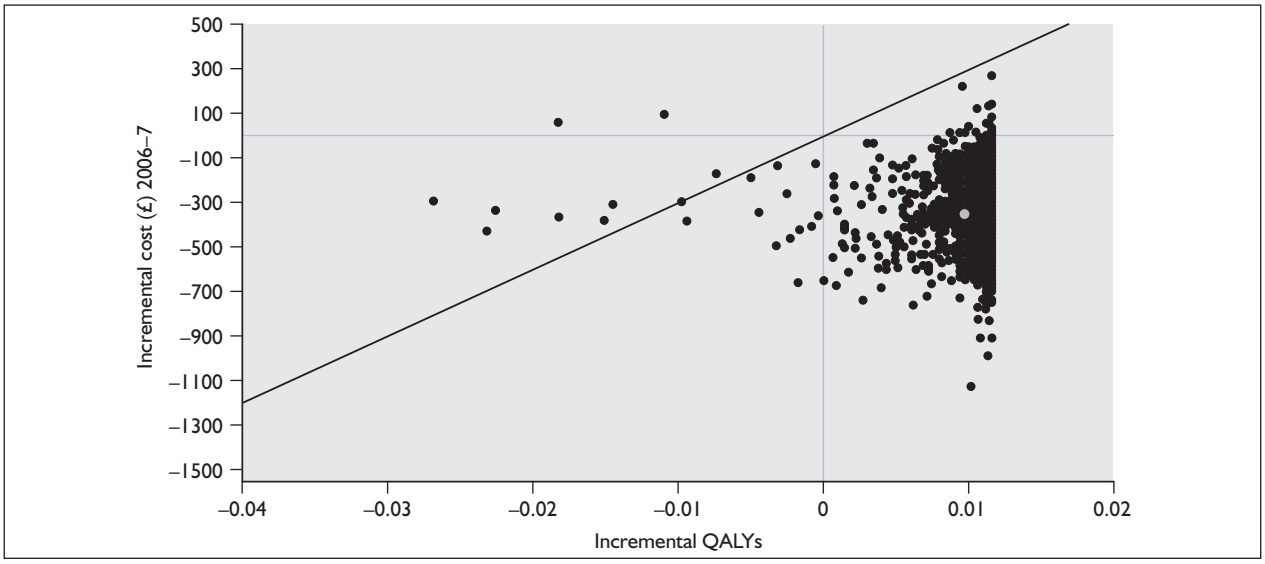


***FIGURE 12*** *Incremental cost-effectiveness plane – worst-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

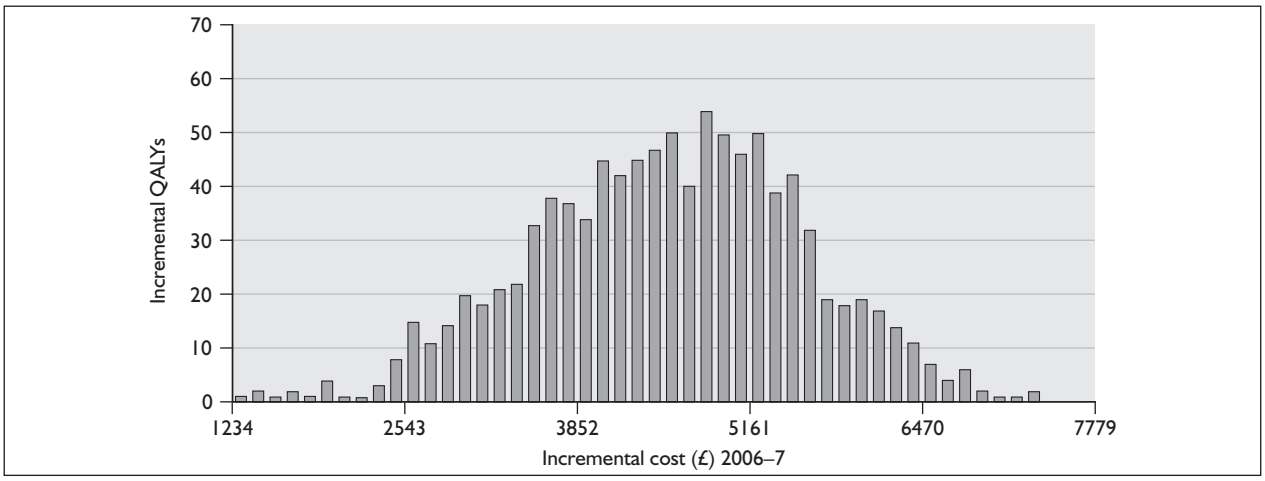


***FIGURE 13*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – best-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

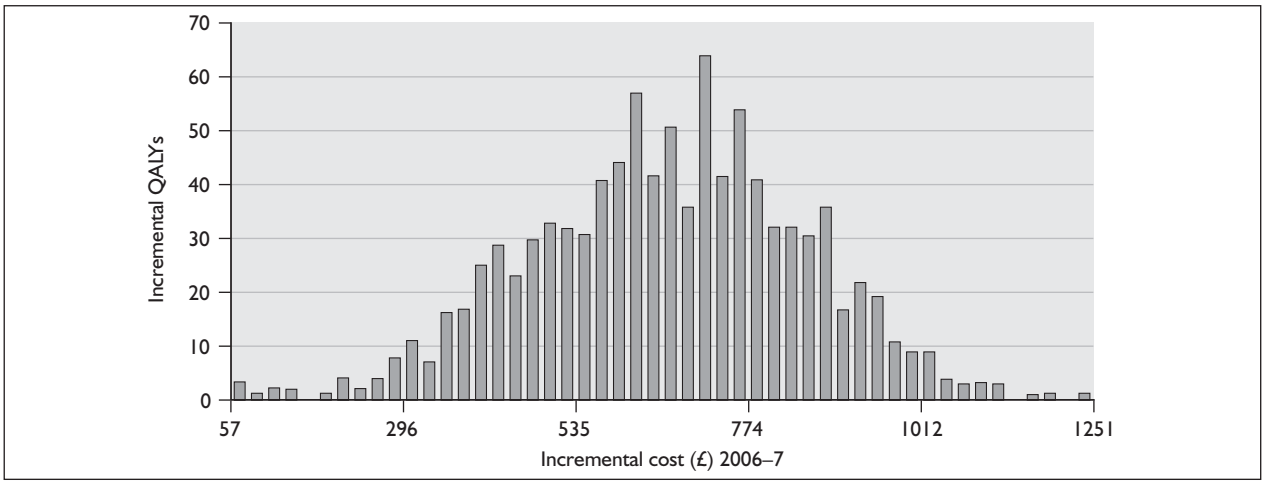


***FIGURE 14*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – worst-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

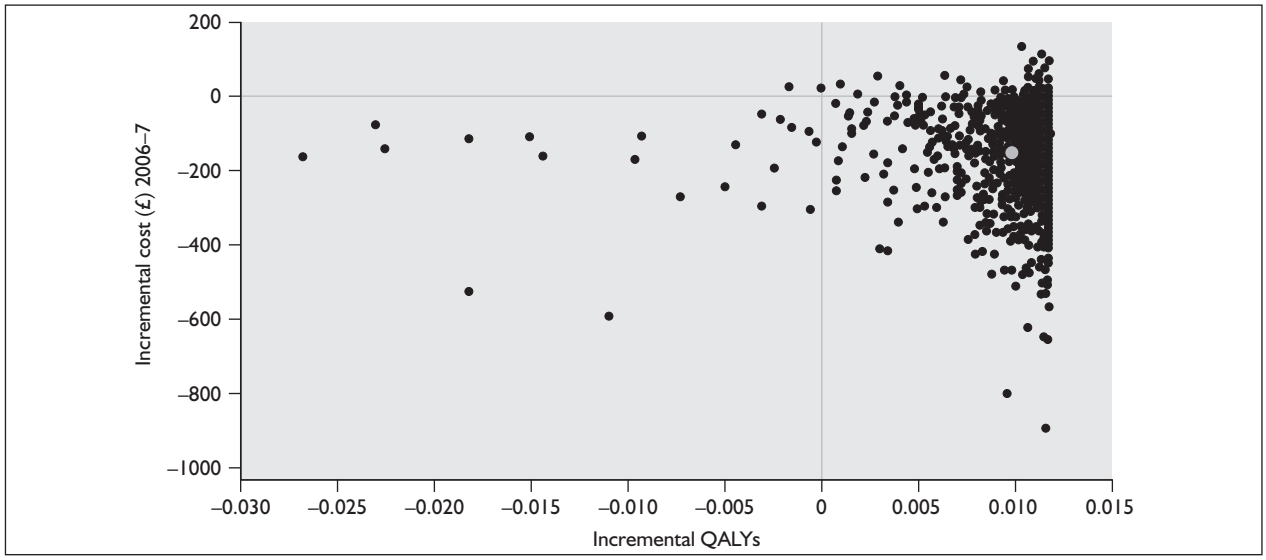


***FIGURE 15*** *Incremental cost-effectiveness plane – sensitivity analysis using AHRQ meta-analysis on length of stay: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

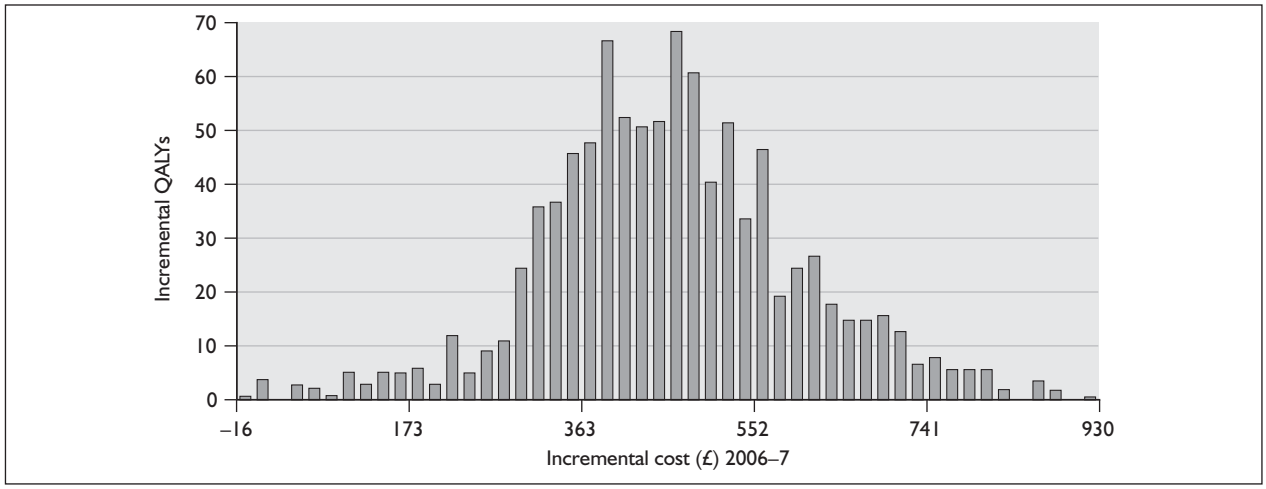


***FIGURE 16*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – sensitivity analysis using AHRQ meta-analysis on length of stay: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for high-risk surgical patients.*

to −1.68) can be observed. The difference in mortality is not statistically significant as the confidence intervals are sufficiently wide to favour any of the comparators (OR 0.81, 95% CI 0.23–2.77). The same analyses as used previously were undertaken in this case.

*Figures 17* and *18* show the results for best- and worst-case ODM scenarios, respectively. In both these figures more than half of the iterations from the Monte Carlo simulation are in the second quadrant (i.e. ODM is more effective and less costly); therefore, no matter how much the decision-maker would value a QALY gained, these results will always favour the ODM strategy. The remainder of the iterations are mainly in the third quadrant, where ODM is both less costly and less effective. Consequently, cost-effectiveness for these results will depend on how much society values the QALY gain from not using ODM. For the £30,000 threshold (black line), in the majority of these iterations the use of ODM would be considered cost-effective (i.e. the circles are to the right of and below the threshold line).

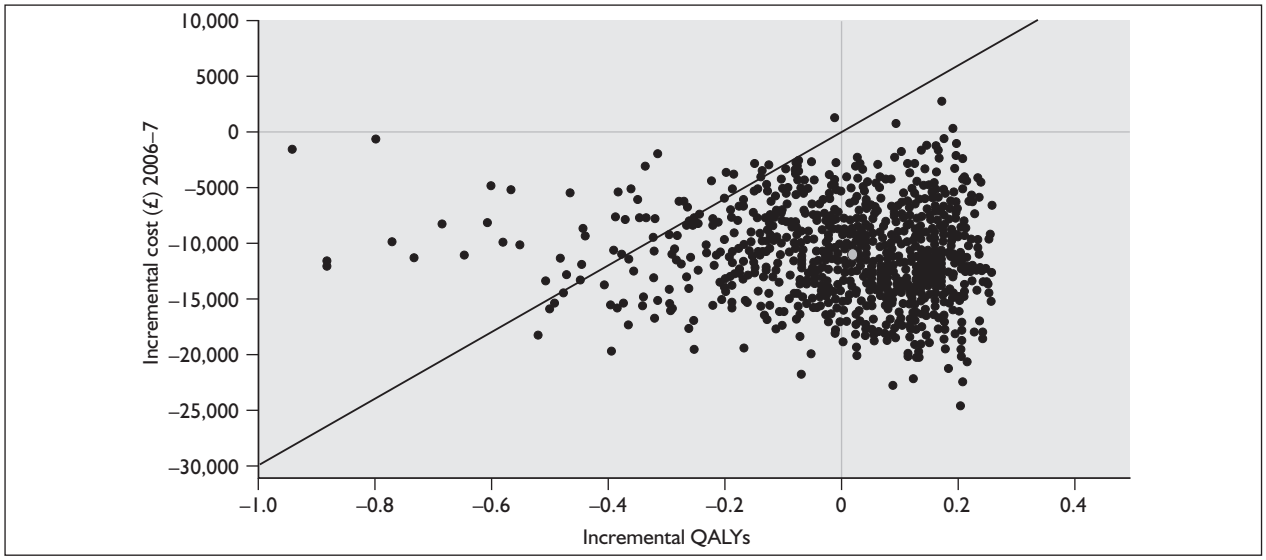


***FIGURE 17*** *Incremental cost-effectiveness plane – best-case ODM scenario: ODM + conventional clinical assessment vs conventional clinical assessment for high-risk surgical patients.*

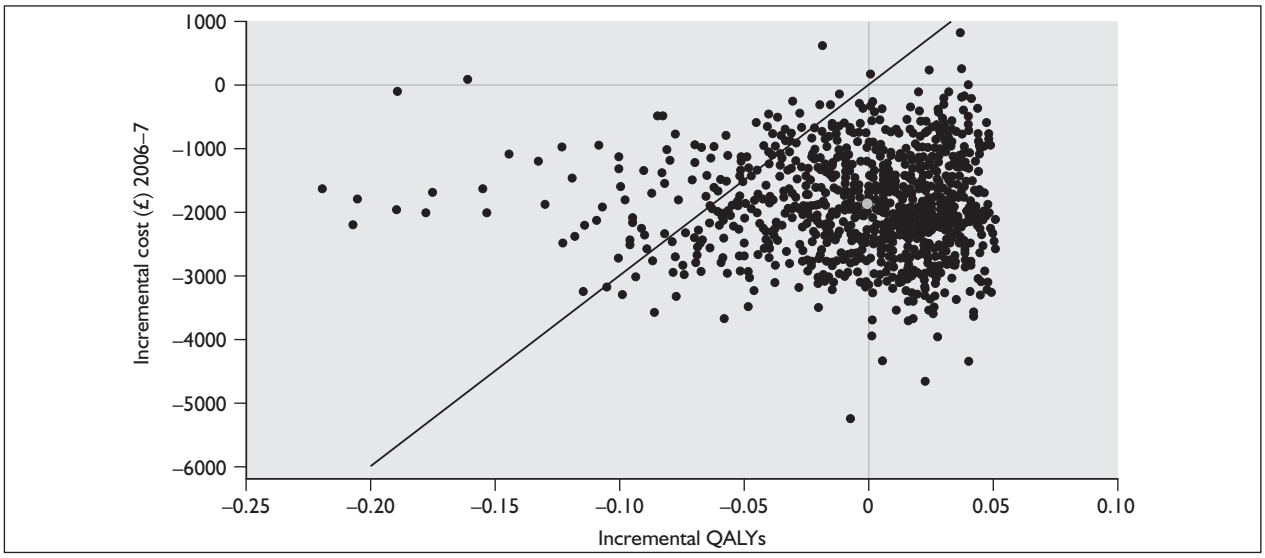


***FIGURE 18*** *Incremental cost-effectiveness plane – worst-case ODM scenario: ODM + conventional clinical assessment vs conventional clinical assessment for high-risk surgical patients.*

*Figures 19* and *20* show the histograms for the average extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective for the best- and worst-case scenarios, respectively. For the best-case scenario a mean extra cost of £11,588 (95% CI −£2529 to £25,705) is needed for ODM to stop being considered cost-effective, while a mean extra cost of £1879 (95% CI −£920 to £4678) would be required for the worst-case scenario.

## Critically ill patients

### *ODM plus CVP plus conventional clinical assessment versus CVP plus conventional clinical assessment for critically ill hospitalised patients*

*Table 12* shows the balance sheet for ODM plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment for critically ill hospitalised patients. In favour of ODM the reduction in total complications (OR 0.49, 95% CI 0.30–0.81) and the reduction in length of stay (1–2 days less) were stated; while

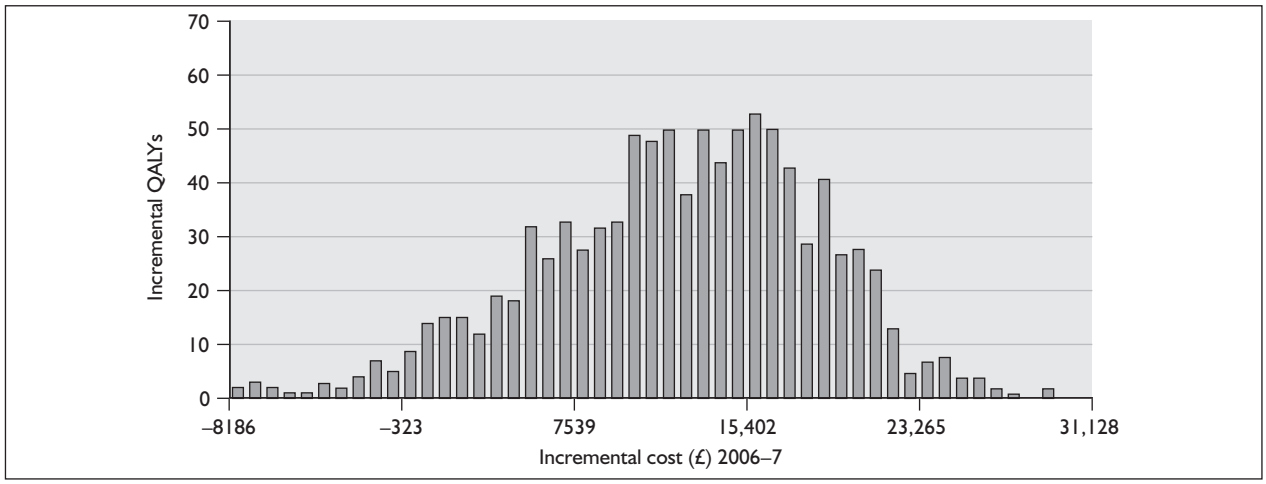


***FIGURE 19*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – best-case ODM scenario: ODM + conventional clinical assessment vs conventional clinical assessment for high-risk surgical patients.*

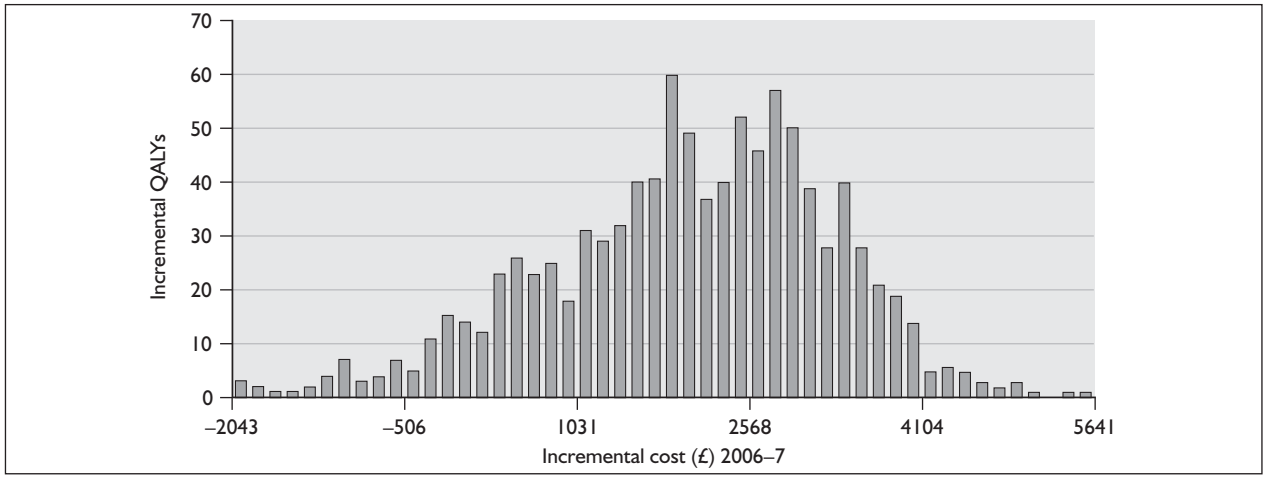


***FIGURE 20*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – worst-case ODM scenario: ODM + conventional clinical assessment vs conventional clinical assessment for high-risk surgical patients*

there was no statistically significant difference in mortality (OR 0.84, 95% CI 0.41–1.70) and it was not possible to measure the effects on other outcomes.

*Figures 21* and *22* show the results of the probabilistic analyses for the best- and worst-case scenarios, respectively. The variability in the cost results comes from the uncertainty in the length of stay estimation. As there were no data to attach a probability distribution to this parameter, an assumption about the difference in length of stay was made. Differences of 2 days and 1 day in length of stay in favour of ODM were assumed for the best- and worst-case scenarios, respectively (it is for this reason that there is almost no variability in incremental cost in the probabilistic analysis). There is variability in QALYs, however, as estimates of the differences in mortality were available.

Almost 70% of the Monte Carlo simulation iterations lie within the second quadrant (i.e. ODM is more effective and less costly). The remaining 30% of the results lie in the third quadrant (i.e. ODM is less effective and less costly). Therefore, the decision as to whether they are cost-effective is independent of the threshold. For the best-case scenario for ODM the probability of being cost-effective at a £30,000 threshold is 90% (80% for worst-case ODM scenario).

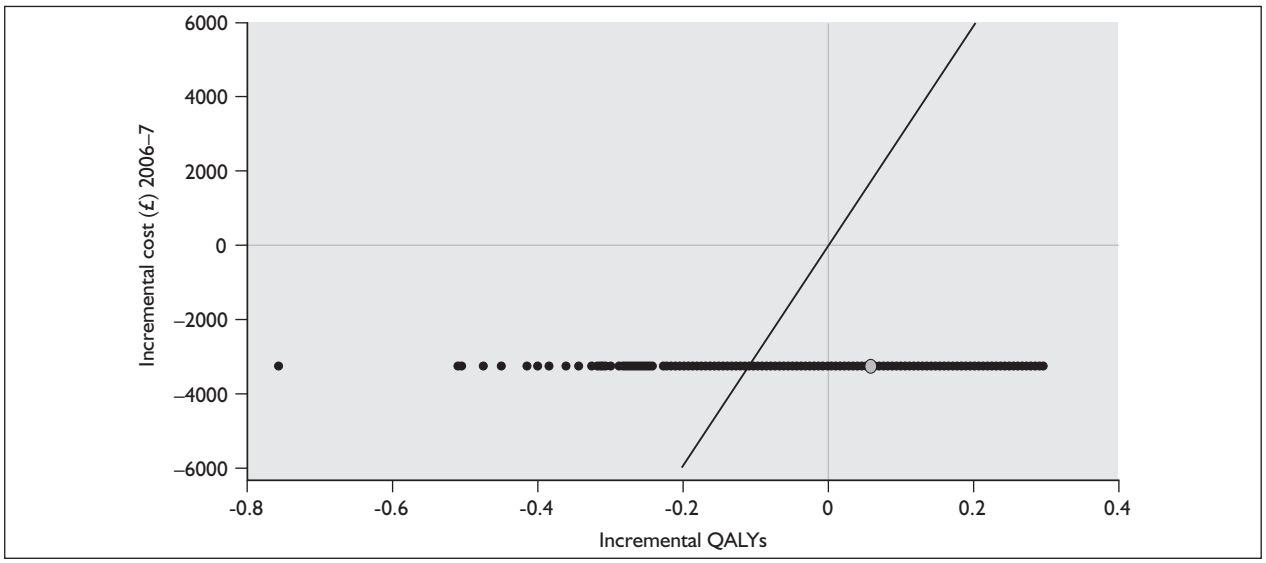


***FIGURE 21*** *Incremental cost-effectiveness plane – best-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for critically ill patients.*

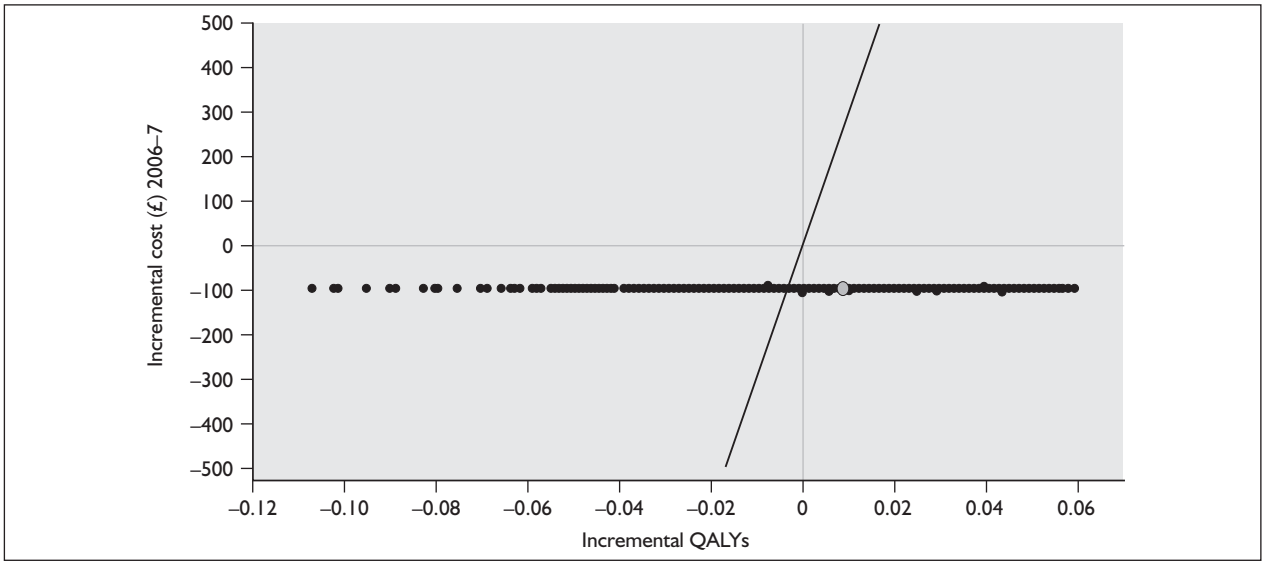


***FIGURE 22*** *Incremental cost-effectiveness plane – worst-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for critically ill patients.*

*Figures 23* and *24* show the histograms for the average extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective for the best- and worst-case scenarios, respectively. For the former, a mean additional cost of £4978 (95% CI −£2655 to £12,611) would be needed for ODM to stop being considered cost-effective; while for the latter, a mean additional cost of £364 (95% CI −£1271 to £1998) would be needed for ODM to stop being considered cost-effective.

## Summary

This chapter explored the cost-effectiveness of ODM and thus expanded upon the work presented in previous chapters. However, it was not possible to obtain quantitative results for all four comparisons for which balance sheets were produced in Chapter 4 and for those where it was possible, results should be interpreted with caution as the results presented in this chapter are subject to the same caveats as those noted in earlier chapters.

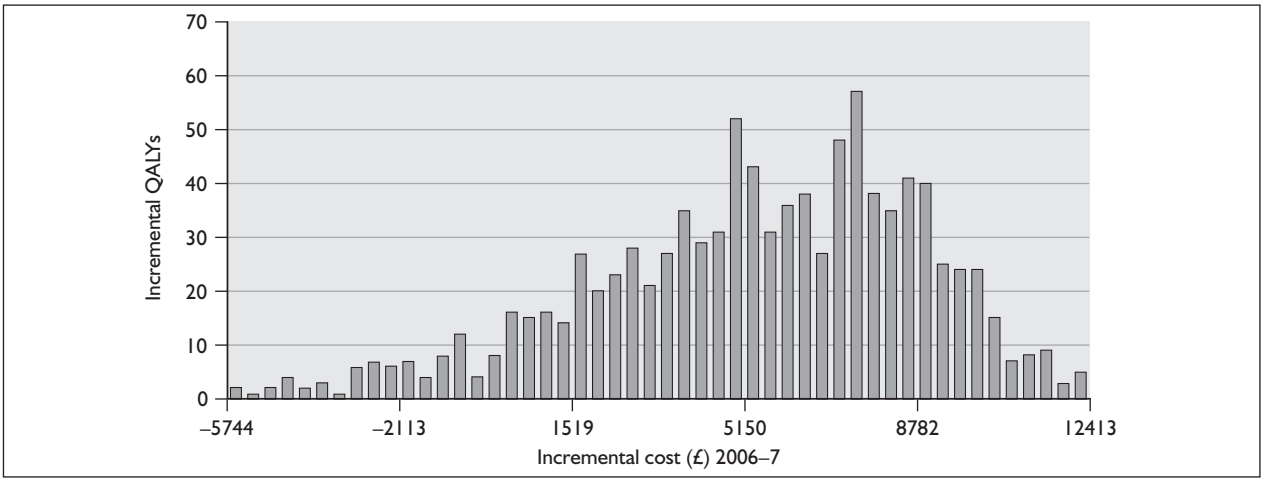


***FIGURE 23*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – best-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for critically ill patients.*

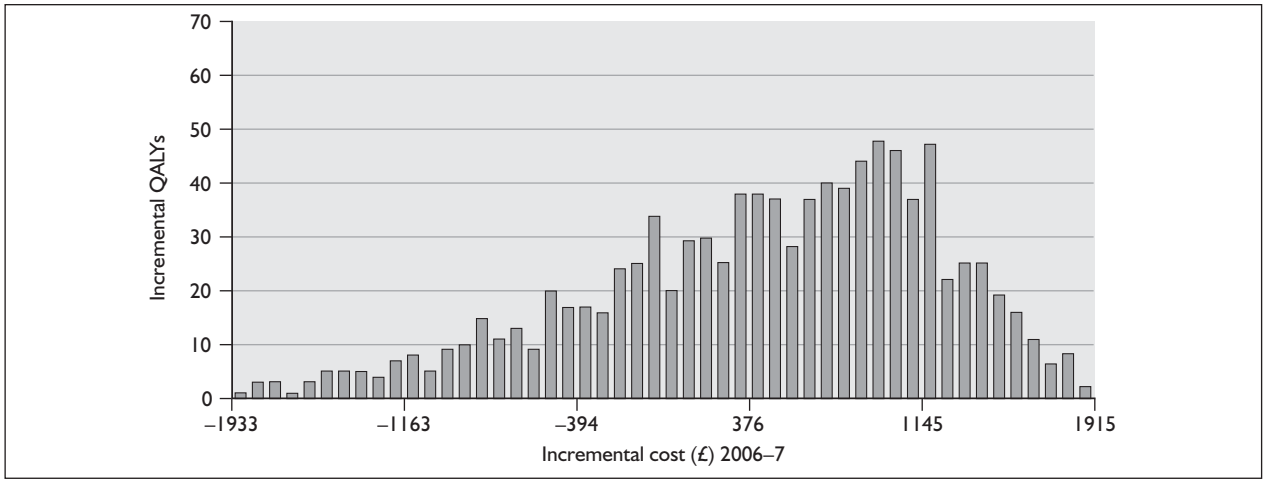


***FIGURE 24*** *Histogram: extra NHS survival costs for ODM to stop being considered cost-effective – worst-case ODM scenario: ODM + CVP + conventional clinical assessment vs CVP + conventional clinical assessment for critically ill patients.*

For high-risk patients we obtained quantitative results for ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment and for ODM plus conventional clinical assessment versus conventional clinical assessment. For critically ill hospitalised patients we obtained quantitative results for ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment only. No quantitative results were obtained for ODM plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment for high-risk surgical patients.

All the comparisons exploring the strategies that involved the use of ODM seem to have a reasonable chance of being considered cost-effective given the assumptions that we have made. However, these results seem to be heavily dependent on the mean cost for the NHS of treating those extra survivors and on the cost of treatments incurred because of monitoring. The threshold value that these costs would need to reach before ODM might not be considered cost-effective ranged from £581 to £11,600 depending on the comparison and the underlying assumptions. It is not clear from this current work whether or not costs of this magnitude are likely to exist in practice.

There are further limitations to these analyses; the main one, perhaps, being the partial modelling approach adopted here. The analyses did not take into account other factors presented within

the balance sheets. This would not affect every comparison in the same way. For instance, factors such as the reduction in major and total complications are definitely in favour of ODM (i.e. higher quality of life for those not having these major complications) for the ODM plus CVP monitoring plus conventional clinical assessment within surgery comparison. Therefore, including these into a full economic model would improve the cost-effectiveness of ODM (however, part of the effect of complications within the model should have been reflected within length of stay differences). For the other comparisons it is unclear what the effect would be of including these additional factors into an economic model.

Finally, as stated earlier in this report, the cost-effectiveness of any strategy depends on the alternative strategies with which it is being compared. For this reason, a full economic model should include all the relevant alternatives; these are all the potential relevant pathways of care that include and do not include ODM, as well as current practice.

# Chapter 6
# Discussion

The original protocol for this study proposed to conduct a systematic review of the RCTs comparing ODM with no cardiac output monitoring perioperatively among patients undergoing major surgery, and with other methods of monitoring heart function (see Appendix 1 for the protocol). A recent systematic review focusing on the safety and effectiveness of ODM was identified after this protocol was finalised but before the project was started. Following discussion with the NCCHTA it was agreed that the Aberdeen TAR group should base its review on the evidence contained in the AHRQ report, supplemented by any additional studies identified, should the AHRQ report be judged to be of sufficiently high quality. Had the review been judged not to be good enough this study would have followed the plan set out in our original protocol.

## Statement of principal findings

### Review of effectiveness

This review is based on the AHRQ report with eight included RCTs, supplemented by two additional RCTs identified, by the Aberdeen group that assessed the effects of ODM-guided fluid administration in patients during surgery (AHRQ report key question 2) or during critical care (AHRQ report key question 3). Studies assessing ODM in patients during surgery reported data for three comparisons:

1. ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment (five studies involving 453 patients)
2. ODM plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment (one study involving 61 patients)
3. ODM plus conventional clinical assessment versus conventional clinical assessment (two AHRQ studies involving 99 patients and one additional study involving 40 patients).

No studies were identified that compared different methods of ODM.

It should be noted that cardiac and non-cardiac surgery (major general, gynaecological, urological, vascular and orthopaedic surgery) are usually not considered together when analysing outcomes as they are considered non-comparable groups of patients owing to differences in type of surgery and presence of co-morbidities, etc. In this study, the results from the one study among cardiac surgery patients[20] has been included in the review and generally reported results consistent with those from the other studies.

Studies assessing ODM in patients in critical care reported data for only one comparison: ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment (one AHRQ study involving 174 patients and one additional study involving 162 patients). The patient groups in these two studies were quite different. One study investigated patients in a cardiac care unit post cardiac surgery, and the other focused on patients suffering from major trauma.

The AHRQ report considered four outcomes: mortality, major complications, total complications and length of hospital stay; data were extracted from the additional studies on these four outcomes. Data were also sought on a fifth outcome, quality of life, from both the studies included in the AHRQ report and the studies identified by our additional searches.

In terms of total mortality, across all comparisons fewer patients in the ODM group died. The exceptions to this were the study by Venn and colleagues[23] comparing ODM plus conventional clinical assessment with conventional clinical assessment during surgery, and the study by McKendry and colleagues[19] comparing ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment following cardiac surgery. The AHRQ report stated that, as the total number of deaths was too low to allow pooling and none of the individual studies showed a statistically significant between-group difference, the evidence was insufficient to allow conclusions to be reached concerning relative mortality rates for any of the

comparisons.[6] A meta-analysis (Peto method) undertaken by the Aberdeen group of the five studies reporting ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment did show statistically significantly fewer deaths in the ODM group (OR 0.13, 95% CI 0.02–0.96). However, as the number of deaths was low and the total combined sample size was still modest, these results should be interpreted with caution.

Major complications were only reported for one comparison: ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment for patients undergoing surgery. All three studies reporting this outcome showed a statistically significant reduction in the rate of major complications and the AHRQ report stated that the strength of evidence supporting this conclusion was strong.[6] A meta-analysis undertaken by the Aberdeen group of the three studies reporting this outcome showed statistically significantly fewer major complications in the ODM group (OR 0.12, 95% CI 0.04–0.31).

In terms of total complications, across all comparisons fewer patients in the ODM group experienced complications, with some studies showing statistically significant differences. The AHRQ report stated that for the comparison of ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment in patients undergoing surgery, the ODM group experienced a clinically significant reduction in the rate of total complications and that the strength of evidence supporting this conclusion was strong.[6] A meta-analysis undertaken by the Aberdeen group of the three studies reporting this outcome showed statistically significantly fewer complications in the ODM group (OR 0.43, 95% CI 0.26–0.71). The AHRQ stated that for all of the other comparisons no conclusions could be reached owing to the small number of studies reporting this outcome, with none reporting a statistically significant between-group difference. However, for the comparison of ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment during hospitalisation, including the additional study by Chytra and colleagues[25] with that of McKendry and colleagues,[19] a meta-analysis undertaken by the Aberdeen group showed a statistically significant reduction in total complications in terms of patient numbers in the ODM group (OR 0.49, 95% CI 0.30–0.81).

In terms of length of hospital stay, the AHRQ report stated that the comparison of ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment in patients undergoing surgery showed a reduced length of hospital stay for the ODM group, and that the strength of evidence supporting this conclusion was strong.[6] The precise magnitude of the reduction is uncertain and the meta-analysis undertaken by the Aberdeen group reported in Chapter 3 for this comparison needs to be interpreted very cautiously. The AHRQ report also stated that the comparison of ODM plus conventional clinical assessment versus conventional clinical assessment during surgery showed a reduced length of stay for the ODM group, although the strength of evidence supporting this conclusion was weak.[6] The additional study by Dodd and colleagues[26] also reported a shorter length of stay for the ODM group.

The AHRQ report stated that because only one small study compared ODM plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment during surgery, and another small study compared ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment during hospitalisation, no conclusions were possible for these comparisons.[6] However, although there was no statistical difference between the groups in the study reporting the former comparison, for the latter comparison both the study included in the AHRQ report and the additional study by Chytra and colleagues[25] reported a statistically significantly shorter median length of hospital stay for the ODM group.

The AHRQ report also considered which ODM-related complications had been reported in the literature (AHRQ report key question 4), with studies of any design considered. Study designs other than RCTs were not considered eligible for our review but collectively these different study designs provide a good indication of the safety of ODM. Twenty-three studies addressed this question, including four RCTs,[17,21–23] 18 case series[7,10,11,34–48] and one article containing two case reports.[49] Three case series[11,39,42] and the article containing two case reports[49] reported minor patient-related complications associated with oesophageal Doppler probes. Nineteen studies involving 654 patients specifically stated that there were no ODM-related complications. The AHRQ report stated that currently no serious adverse events had been reported in the literature and

concluded that the available evidence suggested that ODM probes were relatively low-risk devices.[6] Of the 10 studies included in this review, five (Chytra,[25] Conway,[17] Noblett,[21] Sinclair[22] and Venn[23]) (including four referred to above and one of the additional studies identified) reported that no ODM-related complications occurred. The remaining five studies (Dodd,[26] Gan,[18] McKendry,[19] Mythen[20] and Wakeling[24]) made no mention of ODM-related complications.

None of the studies reported quality of life data, although the study by Wakeling and colleagues[24] did state that the EORTC QLQ-C30 and QLQ-CR38 quality of life questionnaires, completed 4–6 weeks after surgery, showed no differences between the groups.

## Review of cost-effectiveness

No economic evaluations relevant to this review were identified. Information reported on the website www.reducinglengthofstay.org.uk[50] has suggested that the use of ODM in one NHS hospital has saved approximately £1M a year since 2004, mainly as a result of the need for less postoperative care. The formal analyses underpinning such information, however, are not readily available. Nevertheless, despite the absence of formal evaluations, information was available from the review of effectiveness for measures of effectiveness and cost-generating events (e.g. length of stay, risk of complications). These data, along with some initial consideration of resources required to provide ODM or its alternatives, were organised in a series of balance sheets so that choices and trade-offs between alternative courses of action could be highlighted.

Very simply, these balance sheets show those factors that favour the use of ODM and those factors that favour the alternative. They also highlight those factors for which we are currently unsure whether they favour ODM or not. As highlighted above, the evidence base for some comparisons is limited. In the high-risk surgical patient population, from the comparison of ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment, it appears likely that ODM is more effective and that the savings made by a reduced length of stay would more than offset the cost (in terms of staff, equipment and consumables) of the set-up and use of ODM. In terms of the comparison of ODM plus conventional clinical assessment with conventional clinical assessment alone, it is likely that the savings made as a result of reduced hospitalisation would offset the costs of ODM. However, in this situation the overall difference in costs and effectiveness is unclear as there is insufficient evidence regarding the effect on mortality and complications. Where data are available the confidence intervals are sufficiently wide to cover clinically and economically important differences that might favour either intervention. The balance sheet for the comparison of ODM plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment really serves only to highlight the need for more evidence with respect to this comparison.

Where ODM might be used in the care of critically ill patients, data were available for only one comparison: ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment. Furthermore, the patient groups from the two identified studies were different. One study considered patients cared for in a cardiac care unit following cardiac surgery and the other considered patients with major trauma. For this comparison it is likely that the reductions in length of stay would compensate for the cost of ODM and that the use of ODM would reduce the incidence of complications, but the effect on mortality is uncertain.

Although it has been argued that the use of ODM may not be associated with a net increase in cost to the NHS, this is based on the assumption that the savings associated with a reduced length of stay can be freed up to pay for the ODM. In reality this is unlikely to happen, but the use of ODM does release the hospital beds for other patients. The net financial cost of ODM is unclear at present, as although ODM equipment and consumables would need to be purchased, fewer consumables and less equipment may be required for other monitoring and for the management of complications.

No evidence was identified relevant to the comparison of pulse contour analysis monitoring. This is not altogether surprising given the relatively recent growth in this technology.

## Economic modelling

The scope for a formal economic model was explored using information from the balance sheets. It was plausible to develop partial models for three of the four comparisons for which balance sheets were constructed (ODM plus CVP

monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment, and ODM plus conventional clinical assessment versus conventional clinical assessment, for high-risk surgical patients; and ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment comparison only, for critically ill hospitalised patients). These are partial models in the sense that they only take into account differences in mortality and length of stay and do so only for those strategies compared in the balance sheets. Results were expressed in terms of additional cost per QALY gained and the average extra cost per additional survivor that would need to be incurred before ODM would no longer be considered cost-effective. ODM best-case and worst-case scenarios were constructed and probabilistic analyses conducted.

For the three comparisons the likelihood for the use of ODM being cost-effective seems high given the comparators and the underlying assumptions within the analyses (e.g. limitations and caveats of the data used in the analyses). Results also depend on the cost to the NHS of treating the extra survivors and the costs of interventions prompted by the monitoring. The magnitude that these costs would need to reach before ODM might not be considered cost-effective ranged from £581 to £11,600 depending on the comparison and the underlying assumptions.

## Strengths and limitations

The strengths of this review include the fact that the AHRQ report upon which it is based is a high-quality study (scored as 5, 'minor bias' on the Oxman and Guyatt systematic review checklist). Also, an additional two studies were identified to add to the evidence base of the eight studies included in the AHRQ review. In addition, all included studies were RCTs, which are less prone to bias than non-randomised study designs, and the outcomes assessed were all patient related.

As noted above there may be some concerns about combining data relating to cardiac surgery patients with data relating to non-cardiac surgery patients. In terms of the use of ODM during surgery the results from both groups of patients are broadly consistent. However, it is less clear whether it is appropriate to combine the data from the two studies identified that considered using ODM among critically ill patients, as the patient groups in these two studies are different.

In terms of limitations, both the AHRQ report and this review excluded non-English language studies. Of the eight studies included in the AHRQ report and the two additional studies identified, five involved fewer than 100 patients. Only 2 of the 10 studies assessed ODM in critical illness. The AHRQ review's outcomes were broadly similar to those included in the original protocol for this review, with the exception of quality of life, which the AHRQ report did not include as an outcome. However, none of the included studies assessing ODM during surgery or postoperatively reported quality of life data.

A limitation of the technology noted by Chytra and colleagues was that in their study of ODM during critical illness it was difficult to keep the Doppler probe in the correct position without frequent adjustments during the 12-hour period that it was being assessed in the ICU.[25] The authors also found the 12-hour study protocol to be time consuming and noted that it would not have been feasible without the co-operation of nursing staff. Gan and colleagues stated that there was a learning curve to achieve placement of the probe to capture the maximal signal.[18] A study by Lefrant and colleagues recommended a period of training involving no more than 12 patients to ensure reliability of cardiac output measurements by ODM.[7]

Other reviews of fluid optimisation interventions have been published that reported patient-related outcomes. A Cochrane review by Price and colleagues[51] included RCTs comparing a fluid optimisation intervention with normal practice or with another fluid optimisation intervention in patients undergoing surgery to repair proximal femoral fracture. The review included two studies, by Sinclair and colleagues[22] and Venn and colleagues,[23] both of which are included in the AHRQ report. The Cochrane review concluded that invasive methods of fluid optimisation during surgery may shorten hospital stay but that their effects on other important, patient-centred, longer-term outcomes are uncertain.[51]

A review by Bundgaard-Nielsen and colleagues[52] assessed the influence of goal-directed therapy on postoperative outcome. Nine studies met the inclusion criteria; the eight reporting ODM were those included in the AHRQ report and the ninth

was a study by Pearse and colleagues[53] comparing LiDCO with CVP monitoring. Pearse and colleagues[53] concluded that goal-directed therapy reduces hospital stay, postoperative nausea and vomiting and complications, and facilitates faster gastrointestinal functional recovery.

With regard to the cost-effectiveness data the primary limitation is the lack of existing studies, which restricts the analysis of cost-effectiveness. Nevertheless, merely by organising the available data some reasonably firm conclusions could be drawn and the choices and trade-offs could be highlighted. Any judgements that utilise these data should consider the pros and cons for the use of ODM as well as the importance of the considerable uncertainty surrounding the estimates of relative effectiveness. Currently, these judgements must be based on the implicit valuation of these factors, but a more explicit consideration could be provided by using the available data within a modelling exercise. Such an exercise was explored and involved the more formal consideration of costs and partially incorporated the best available evidence on effectiveness. The added value of such work might be seen as limited for some comparisons, such as ODM plus CVP monitoring and conventional clinical assessment versus plus CVP monitoring and conventional clinical assessment, where conclusions could potentially be reached already. The modelling exercise incorporated some of the uncertainty around effectiveness estimates and shed some light on the extent to which the use of ODM might be considered cost-effective. A full economic model might serve further to inform the decision-making process by entirely incorporating other factors (e.g. number of major and/or total complications) for all the relevant alternatives, and not only employing those pairwise comparisons considered in the partial modelling exercises. Cardiac monitoring can be used in a variety of patient groups. It is possible that the cost-effectiveness (and the effectiveness) may differ between these groups. An indication for this is the evidence of heterogeneity identified in *Figure 7*.

## Uncertainties

In terms of the type of patients considered to be suitable for ODM-guided fluid administration during surgery, the AHRQ report stated that its conclusions applied only to patients undergoing surgical procedures with an expected substantial blood loss or fluid shifts requiring fluid replacement. The types of surgery performed in the seven AHRQ and one additional study assessing ODM during surgery included moderate- to high-risk procedures such as elective bowel surgery, hip fracture repair surgery, elective cardiac surgery, elective general, urological or gynaecological surgery, and major general abdominal surgery.

The optimal period of ODM-guided fluid administration once patients have been admitted to critical care following surgery is unclear. McKendry and colleagues[19] applied ODM-guided fluid administration for a period of 4 hours after patients were admitted to cardiac intensive care after cardiac surgery, while Chytra and colleagues[25] monitored multiple-trauma patients with major blood loss for a period of 12 hours following admission to the ICU.

All of the included studies involved unconscious patients, as ODM technologies currently in practice are unsuitable for use in postoperative awake patients. Although an ODM probe is now manufactured for per-nasal passage in awake patients it has yet to be fully evaluated and no additional studies using such a probe were identified that met our inclusion criteria.

In terms of cost-effectiveness, limited data are currently available. While it may be possible to draw some sensible conclusions about the use of ODM, additional research may be useful both in terms of using the available data more fully in an economic modelling exercise and to fill gaps in the primary research evidence.

## Other relevant factors

Potentially relevant studies identified from a search of the National Research Register are listed in Appendix 9. The largest of the ongoing studies is a French multicentre study (Cholley) that is scheduled to run from April 2007 to April 2010. This study was also mentioned in the AHRQ report. The aim of the study is to assess whether intraoperative fluid supplementation to improve tissue perfusion can reduce the incidence of postoperative complications in elderly patients with hip fracture. The study design is described as randomised, double-blind and placebo controlled. The primary end point is to demonstrate that colloid titration, guided using oesophageal

Doppler estimation of stroke volume, during the surgical repair of hip fracture reduces the incidence of postoperative complications. Secondary end points include (a) delay to walking without help; (b) increased number of days 'out of hospital' at 3 months after the fracture; and (c) mortality at 1 year. The protocol for the study indicated that 19 centres would be participating and that the aim was to recruit 800 patients. This will be the largest study of ODM during surgery to date and its results should add substantially to the existing evidence base.

# Chapter 7
# Conclusions

## Implications for practice

### Safety

No serious, and only a few minor, patient-related complications associated with ODM probes appear to have been reported and the available evidence suggests that ODM probes are relatively low-risk devices. Therefore, the use of ODM might be considered safe.

### Effectiveness and cost-effectiveness

The evidence base on effectiveness, based on the randomised evidence, is limited. Furthermore, there are no published cost-effectiveness analyses. Nevertheless, despite the limited evidence it is possible to draw out some implications for practice. These have been grouped around the four strategies for the use of ODM that have been considered.

#### *Use of ODM for high-risk surgical patients*

Evidence for three different comparisons involving the use or non-use of ODM in this group of patients was available and in all three cases appeared relevant to the NHS. The available evidence from five studies involving 453 patients suggests that the addition of ODM-guided fluid administration to CVP monitoring plus conventional assessment during surgery results in fewer major and total complications and a shorter length of hospital stay, and possibly fewer deaths, with pooled estimates for all outcomes showing a statistically significant difference in favour of the ODM group. Given these data it is quite plausible that the use of ODM in this situation would be less costly and more effective.

For the single study ($n = 61$) reporting ODM plus conventional assessment versus CVP monitoring plus conventional assessment during surgery, although all of the outcomes reported favoured the ODM group none were statistically significant. Therefore, no conclusions are possible for any of the outcomes reported in this comparison. Insufficient evidence is available to draw any robust conclusions about cost-effectiveness for this comparison.

None of the three studies ($n = 139$) reporting ODM plus conventional clinical assessment versus conventional clinical assessment during surgery showed a statistically significant difference for mortality; none reported the outcome of major complications; one reported total complications (a non-statistical difference favouring the ODM group); and all three reported a shorter length of stay for the ODM group, reaching statistical significance in one study. The addition of ODM to conventional assessment during surgery may lead to a shorter length of hospital stay. However, this conclusion is based on limited evidence from only three small studies and no conclusions are possible for the other outcomes. Again, only limited evidence is available on the cost-effectiveness of using ODM in this situation. On balance it would appear likely that the cost of ODM would be more than compensated for by the reduction in length of stay. However, the overall effect on costs is uncertain. As described above, owing to the limited evidence, firm data on measures of clinical effectiveness (some of which are also cost drivers) are not available. Therefore, should ODM be adopted, a judgement would be needed on whether the trends in favour, observed for other comparisons, would be maintained for this comparison.

#### Summary of evidence for the use of ODM in high-risk surgical patients in the NHS

The addition of ODM-guided fluid administration combined with CVP monitoring plus conventional assessment during major surgery results in fewer complications, a shorter length of hospital stay and possibly fewer deaths, and may be a cost-effective use of resources in the NHS.

#### *Use of ODM in the critically ill*

Neither of the two studies ($n = 336$) reporting ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment during hospitalisation showed a statistically significant difference in mortality, and neither reported major complications; therefore, no conclusions are possible for these outcomes. However, the addition of ODM to CVP monitoring plus conventional

assessment may lead to fewer total complications and a shorter length of hospital stay. In a meta-analysis of the outcome of total complications, the pooled estimate showed a statistically significant difference in favour of the ODM group. Both studies also reported a statistically significantly shorter median length of stay in favour of the ODM group. However, the evidence for these two outcomes should be treated with caution as it is based on only two studies. Taking this evidence at face value, it would seem likely that the reduction in length of stay would compensate for the cost of using ODM. Furthermore, it seems likely that the use of ODM would be associated with a reduced cost of managing complications (as well as with increased benefit to the patient). Again, however, should ODM be adopted, a judgement would be required on whether the reduction in mortality observed for other uses of ODM would be continued in this setting. A prior judgement is required on whether the evidence base available is sufficient.

**Summary of evidence for the use of ODM in critically ill patients in the NHS**

Although there is some evidence for reduced complication rates and hospital lengths of stay in subgroups of critically ill patients, there is insufficient evidence to recommend the widespread use of ODM in critically ill patients in the NHS.

# Recommendations for research

## Surgery

Well-designed multicentre RCTs are required to address the following questions related to perioperative patients with expected substantial blood loss or fluid shifts requiring fluid replacement and/or with major co-morbidity:

- Does ODM-guided fluid therapy plus conventional clinical assessment improve outcome compared with conventional clinical assessment during major surgery?
- Does ODM-guided fluid therapy plus conventional clinical assessment plus or minus CVP monitoring improve outcome compared with CVP monitoring plus conventional clinical assessment during major surgery?

Studies should have a follow-up period of at least 6 months and should report the following outcomes: mortality (hospital and longer term); length of stay [hospital, critical care (ICU and HDU)]; days of organ support in ICU and HDU; complications (major, total, technology-related); and quality of life in months after hospital discharge.

Further research is required to assess the additional benefit, if any, of ODM-guided fluid administration during surgery and continuing into the early postoperative period versus ODM-guided fluid administration during surgery alone. Further research is also required to determine the optimal number of hours for ODM-guided fluid administration to continue after surgery once the patient has been admitted to a critical care facility.

Given the paucity of the existing economic evidence base, any further primary research should include an economic evaluation or should provide data suitable for use in an economic model.

## Critical illness

A well-designed multicentre RCT is required to address the following question related to subgroups of critically ill patients, particularly those with major trauma and septic shock:

- Does ODM-guided fluid therapy plus conventional clinical assessment plus or minus CVP monitoring improve outcome compared with CVP monitoring plus conventional clinical assessment in critical illness?

Studies should have a follow-up period of at least 6 months and should report the following outcomes: mortality (critical care, hospital and longer term); length of stay [hospital; critical care (ICU and HDU)]; days of organ support in ICU and HDU; complications (major, total, technology-related); and quality of life in months after hospital discharge.

Again, economic evaluations should be conducted as part of this primary research or, at the very least, further primary research should seek to provide data that can be used in an economic model.

# Acknowledgements

We thank all those researchers throughout the world who provided additional information on the trials and registries. We also thank Heather Mackintosh for secretarial support. The Health Services Research Unit and the Health Economics Research Unit are both core funded by the Chief Scientist Office of the Scottish Government Health Directorate. The views expressed are those of the authors.

## Contribution of authors

Graham Mowatt completed the review of effectiveness. Gordon Houston drafted the background chapter and along with Brian Cuthbertson provided advice and commented on drafts of the review. Rodolfo Hernández drafted the decision problem and conducted the economic evaluation. Robyn de Verteuil conducted the review of economic evaluations. Cynthia Fraser developed and ran the search strategies and was responsible for obtaining papers and for reference management. Luke Vale led the review team.

# References


1. Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C *et al*. 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. *Health Technol Assess* 2006;**10**(29).

2. Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ *et al*. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med* 2003;**348**(1):5–14.

3. Improving Surgical Outcomes Group. *Modernising care for patients undergoing major surgery: improving patient outcomes and increasing clinical efficiency.* Reducinglengthofstay.org.uk; 2005. URL: www.reducinglengthofstay.org/isog.html. Accessed June 2007.

4. Cullinane M, Gray AJ, Hargarves CM, Lansdown M, Martin IC, Schubert N. *The 2003 report of the national confidential enquiry into perioperative deaths: who operates when? II.* National Confidential Enquiry into Patient Outcome and Death; 2003. URL: www.ncepod.org.uk/pdf/2003/03full.pdf. Accessed June 2007.

5. *Oesophageal doppler monitoring.* London: National Institute for Health and Clinical Excellence; 2005. URL: http://guidance.nice.org.uk/page.aspx?o=287500. Accessed July 2007.

6. *Esophageal Doppler ultrasound-based cardiac output monitoring for real-time therapeutic management of hospitalized patients.* Rockville, MD: Agency of Healthcare Research and Quality; 2007. Available from: URL: www.cms.hhs.gov/determinationprocess/downloads/id45TA.pdf. Accessed March 2007.

7. Lefrant JY, Bruelle P, Aya AGM, Saissi G, Dauzat M, La Coussaye JE *et al*. Training is required to improve the reliability of esophageal Doppler to measure cardiac output in critically ill patients. *Intensive Care Med* 1998;**24**(4):347–52.

8. Dark PM, Singer M. The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. *Intensive Care Med* 2004;**30**(11):2060–6.

9. Cuschieri J, Rivers E, Caruso J. A comparison of transesophageal Doppler, thermodilution and Fick cardiac output measurements in critically ill patients. *Crit Care Med* 1998;**26**(Suppl 1):A62.

10. Madan AK, UyBarreta VV, Aliabadi-Wahle S, Jesperson R, Hartz RS, Flint LM *et al*. Esophageal Doppler ultrasound monitor versus pulmonary artery catheter in the hemodynamic management of critically ill surgical patients. *J Trauma* 1999;**46**(4):607–11.

11. Singer M, Clarke J, Bennett ED. Continuous hemodynamic monitoring by esophageal Doppler. *Crit Care Med* 1989;**17**(5):447–52.

12. Eagle KA, Berger PB, Calkins H, Chaitman BR, Ewy GA, Fleischmann KE et al. ACC/AHA Guideline update for perioperative cardiovascular evaluation for noncardiac surgery – executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *Circulation* 2002;**105**(10):1257–67.

13. Verhagen AP, de Vet HC, de Bie RA, Kessels AG, Boers M, Bouter LM *et al*. The Delphi list: a criteria list for quality assessment of randomized clinical trials for conducting systematic reviews developed by Delphi consensus. *J Clin Epidemiol* 1998;**51**(12):1235–41.

14. Oxman AD, Guyatt GH. The science of reviewing research. *Ann N Y Acad Sci* 1993;**703**:125–33.

15. Oxman AD. Checklists for review articles. *Br Med J* 1994;**309**(6955):648–51.

16. Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. Systematic reviews of trials and other studies. *Health Technol Assess* 1998;**2**(19):1–276.

17. Conway DH, Mayall R, Abdul-Latif MS, Gilligan S, Tackaberry C. Randomised controlled trial investigating the influence of intravenous fluid titration using oesophageal Doppler monitoring during bowel surgery. *Anaesthesia* 2002;**57**(9):845–9.

18. Gan TJ, Soppitt A, Maroof M, el Moalem H, Robertson KM, Moretti E et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology* 2002;**97**(4):820–6.

19. McKendry M, McGloin H, Saberi D, Caudwell L, Brady AR, Singer M. Randomised controlled trial assessing the impact of a nurse delivered,

flow monitored protocol for optimisation of circulatory status after cardiac surgery. *BMJ* 2004;**329**(7460):258–62.

20. Mythen MG, Webb AR. Perioperative plasma volume expansion reduces the incidence of gut mucosal hypoperfusion during cardiac surgery. *Arch Surg* 1995;**130**(4):423–9.

21. Noblett SE, Snowden CP, Shenton BK, Horgan AF. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006;**93**(9):1069–76.

22. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ* 1997;**315**(7113):909–12.

23. Venn R, Steele A, Richardson P, Poloniecki J, Grounds M, Newman P. Randomized controlled trial to investigate influence of the fluid challenge on duration of hospital stay and perioperative morbidity in patients with hip fractures. *Br J Anaesth* 2002;**88**(1):65–71.

24. Wakeling HG, McFall MR, Jenkins CS, Woods WG, Miles WF, Barclay GR *et al*. Intraoperative oesophageal Doppler guided fluid management shortens postoperative hospital stay after major bowel surgery. *Br J Anaesth* 2005;**95**(5):634–42.

25. Chytra I, Pradl R, Bosman R, Pelnar P, Kasal E, Zidkova A. Esophageal Doppler-guided fluid management decreases blood lactate levels in multiple-trauma patients: a randomized controlled trial. *Crit Care* 2007;**11**(1):R24 (22 February).

26. Dodd TE, McCormack RN, Dorman F, Green R, Bromilow J. Using the oesophageal doppler monitor in elective colorectal surgery [poster presentation]. Annual Meeting of Wessex Anaesthetists in Training. Poole, Dorset; 2004 (October).

27. *NHS economic evaluation database handbook.* University of York: Centre for Reviews and Dissemination; 2007. URL: www.york.ac.uk/inst/crd/pdf/nhseed-handb07.pdf. Accessed June 2007.

28. *Reference costs 2006 collection: costing and activity guidance and requirements.* London: Department of Health; 2006. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4124470. Accessed June 2007.

29. *Scottish health service costs.* ISD Scotland; 2007. URL: www.isdscotland.org/isd/797.html. Accessed July 2007.

30. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*. 3rd edn. Oxford: Oxford University Press; 2005.

31. Information Services Division R040. *Specialty group costs – inpatients in acute specialties*. April 2005–March 2006. URL: www.isdscotland.org/isd/4434.html. Accessed July 2007.

32. Cuthbertson BH, Scott J, Strachan M, Kilonzo M, Vale L. Quality of life before and after intensive care. *Anaesthesia* 2005; 60(4), 332–339.

33. National Institute for Health and Clinical Excellence. *A guide for manufacturers and sponsors*. 2004. URL: www.nice.org.uk/niceMedia/pdf/TAprocessmanual_manufacturers_sponsors.pdf.

34. Bein B, Worthmann F, Tonner PH, Paris A, Steinfath M, Hedderich J *et al*. Comparison of esophageal Doppler, pulse contour analysis and real-time pulmonary artery thermodilution for the continuous measurement of cardiac output. *J Cardiothorac Vasc Anesth* 2004;**18**(2):185–9.

35. Cipolla J, Stawicki S, Spatz D. Hemodynamic monitoring of organ donors: a novel use of the esophageal echo-Doppler probe. *Am Surg* 2006;**72**(6):500–4.

36. Collins S, Girard F, Boudreault D, Chouinard P, Normandin L, Couture P et al. Esophageal Doppler and thermodilution are not interchangeable for determination of cardiac output. *Can J Anaesth* 2005;**52**(9):978–85.

37. Elliott S, Savill P, Eckersall S. Cardiovascular changes during laparoscopic cholecystectomy: a study using transoesophageal Doppler monitoring. *Eur J Anaesthesiol* 1998;**15**(1):50–5.

38. Feldman LS, Anidjar M, Metrakos P, Stanbridge D, Fried GM, Carli F. Optimization of cardiac preload during laparoscopic donor nephrectomy: a preliminary study of central venous pressure versus esophageal Doppler monitoring. *Surg Endosc* 2004;**18**(3):412–16.

39. Iregui MG, Prentice D, Sherman G, Schallom L, Sona C, Kollef MH. Physicians' estimates of cardiac index and intravascular volume based on clinical assessment versus transesophageal Doppler measurements obtained by critical care nurses. *Am J Crit Care* 2003;**12**(4):336–42.

40. Koliopanos A, Zografos G, Skiathitis S, Stithos D, Voukena V, Karampinis A *et al*. Esophageal Doppler (ODM II) improves intraoperative hemodynamic monitoring during laparoscopic surgery. *Surg Laparosc Endosc Percutan Tech* 2005;**15**(6):332–8.

41. Krishnamurthy B, McMurray TJ, McClean E. The peri-operative use of the oesophageal Doppler monitor in patients undergoing coronary artery revascularisation. A comparison with the continuous cardiac output monitor. *Anaesthesia* 1997;**52**(7):624–9.

42. Moxon D, Pinder M, van Heerden PV, Parsons RW. Clinical evaluation of the HemoSonic monitor in cardiac surgical patients in the ICU. *Anaesth Intensive Care* 2003;**31**(4):408–11.

43. Odenstedt H, Aneman A, Oi Y, Svensson M, Stenqvist O, Lundin S. Descending aortic blood flow and cardiac output: a clinical and experimental study of continuous oesophageal echo–Doppler flowmetry. *Acta Anaesthesiol Scand* 2001;**45**(2):180–7.

44. Sawai T, Nohmi T, Ohnishi Y, Takauchi Y, Kuro M. Cardiac output measurement using the transesophageal Doppler method is less accurate than the thermodilution method when changing Paco(2). *Anesth Analg* 2005;**101**(6):1597–601.

45. Seoudi HM, Perkal MF, Hanrahan A, Angood PB, Kirton O, Nyachowe P *et al*. The esophageal Doppler monitor in mechanically ventilated surgical patients: does it work? *J Trauma* 2003;**55**(4):720–6.

46. Sharma J, Bhise M, Singh A, Mehta Y, Trehan N. Hemodynamic measurements after cardiac surgery: transesophageal Doppler versus pulmonary artery catheter. *J Cardiothorac Vasc Anesth* 2005;**19**(6):746–50.

47. Su NY, Huang CJ, Tsai P, Hsu YW, Hung YC, Cheng CR. Cardiac output measurement during cardiac surgery: esophageal Doppler versus pulmonary artery catheter. *Acta Anaesthesiol Sin* 2002;**40**(3):127–33.

48. Valtier B, Cholley BP, Belot J-P, De La Coussaye JE, Mateo J, Payen DM. Noninvasive monitoring of cardiac output in critically ill patients using transesophageal Doppler. *Am J Respir Crit Care Med* 1998;**158**(1):77–83.

49. Chandan GS, Hull JM. Incorrectly placed oesophageal Doppler probe. *Anaesthesia* 2004;**59**(7):723.

50. *Reducing length of stay: case studies*. Reducinglengthofstay.org.uk; 2007. URL: www.reducinglengthofstay.org.uk/casestudies.html. Accessed June 2007.

51. Price JD, Sear JW, Venn RM. *Perioperative fluid volume optimization following proximal femoral fracture*. Cochrane Database of Systematic Review: 2004; Issue 1. Art. No. CD003004. DOI: 10.1002/14651858.CD003004.pub2.

52. Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol Scand* 2007;**51**(3):331–40.

53. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care* 2005;**9**(6):R687–93.

54. *Improving access to cost-effectiveness information for health care decision making: the NHS Economic Evaluation Database*. CRD Report No. 6. York: NHS Centre for Reviews & Dissemination; 2001.

# Appendix 1

# Aberdeen TAR group protocol for systematic review of oesophageal Doppler monitoring

## Date of project

March 2007.

## Title of project

What is the clinical and cost-effectiveness of oesophageal Doppler monitoring in critically ill and high-risk surgical patients?

## Name of TAR team and project 'lead'

Aberdeen Technology Assessment Group

Luke Vale
Senior Research Fellow, Team Leader and Health Economist
Health Services Research Unit/Health Economics Research Unit
University of Aberdeen
Polwarth Building, Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 551127
Fax: 01224 554580
E-mail: l.vale@abdn.ac.uk

*Reserve contact:*
Graham Mowatt
Research Fellow, Senior Systematic Reviewer
Health Services Research Unit
University of Aberdeen
Health Sciences Building, Foresterhill
Aberdeen AB25 2ZD
Tel: 01224 552494
Fax: 01224 554580
E-mail: g.mowatt@abdn.ac.uk

## Summary

It is believed that measuring heart function during critical illness or during surgery can improve patient outcomes. Until recently the main method used to measure heart function has been pulmonary artery catheterisation, although for people undergoing surgery even this approach is uncommon. While providing useful information, PACs have not been shown to improve mortality. This, coupled with concerns over procedural complications associated with the use of these catheters along with the development of less complex heart monitors, has resulted in a global decline in the usage of PACs over recent years.

This review will assess the effectiveness and cost-effectiveness of ODM when used for monitoring heart function in comparison with (a) standard care (i.e. no cardiac output monitor perioperatively among patients undergoing major surgery; and (b) other methods of monitoring heart function such as pulmonary artery catheterisation or pulse contour monitoring devices in critically ill patients or in patients undergoing major surgery.

The analysis will focus on outcomes of most importance to patients (e.g. mortality, length of hospitalisation, length of stay in critical care, days of organ support in ICU and complications). Cost-effectiveness will be assessed from the perspective of the NHS and personal social services.

Information on the relative effectiveness of the alternative interventions will be derived by systematically reviewing relevant RCTs comparing ODM with: (a) standard care (i.e. no cardiac output monitor perioperatively among patients undergoing major surgery); and (b) other methods of monitoring heart function as outlined above. Information on cost-effectiveness will initially be assessed using a systematic review of economic evaluations comparing ODM with the relevant comparators for the two patient groups specified.

## Decision problem

Optimal management of cardiac output and haemodynamic status have long been considered key to improving outcome in critically ill patients and in high-risk patients undergoing major surgery. Traditionally, PACs have been used to monitor cardiac output and haemodynamic status and to guide treatment. A recent HTA Programme-funded study demonstrated that PAC insertion

and management of critically ill patients using the parameters monitored by pulmonary artery catheterisation fails to confer an outcome benefit. Further studies have also cast doubt on the value of PACs in high-risk major surgery.[2] This, coupled with concerns related to procedural complications associated with the insertion and use of the PAC along with the development and assimilation of less invasive cardiac output monitors in clinical practice, has resulted in a global decline in the usage of the PAC in recent years.

Less invasive technologies to monitor cardiac output and other haemodynamic parameters include ODM and systems based on pulse contour analysis and dye dilution methods. Oesophageal Doppler monitoring measures blood flow velocity in the descending thoracic aorta using a flexible ultrasonic probe inserted into the patient's oesophagus. This information is combined with an estimate of aortic cross-sectional area (derived from the patient's age, height and weight), allowing haemodynamic variables to be calculated.

Pulse contour analysis devices employ algorithms to perform real-time continuous monitoring of cardiac output using arterial pulse contour analysis. There are several types of device available, but all require initial calibration which may be by means of either transpulmonary thermodilution or lithium dilution techniques.

Information on the relative effectiveness of the alternative interventions will be derived by systematically reviewing relevant RCTs. Information on cost-effectiveness will be assessed using a systematic review of economic evaluations of the alternative methods.

## Report methods for synthesis of evidence of clinical effectiveness

A review of the evidence for clinical effectiveness will be undertaken systematically following the general principles recommended in the QUOROM statement (URL: www.consort-statement.org/QUOROM.pdf).

### *Nature of existing evidence base and justification of approach taken*

There are at least two existing reviews of ODM. These reviews are not systematic in that they did not use a search strategy likely to identify all relevant studies. They compared ODM primarily with pulmonary artery catheterisation and focused on measures of cardiac output.

However, it is recognised that pulmonary artery catheterisation is an inappropriate gold standard for the measurement of cardiac output[1] and the relationship between these surrogate measures and patient outcomes is unclear. Furthermore, as indicated above, the use of PACs is becoming less common while use of other less invasive cardiac monitoring methods is increasing. For these reasons, we do not propose to update these existing reviews; rather we aim to complete a new systematic review of ODM compared with relevant comparators (including other new methods of measuring heart function) which will focus on the outcomes of most importance to patients.

### *Population*

Inclusion criteria:

- adults being managed in critical care who require cardiac monitoring
- adults during major surgery.

Exclusion criteria:

- use of ODM in patient groups other than those specified above
- studies in which ODM was used as a measure of study outcome rather than as a monitoring tool leading to a clinical intervention.

Relevant subgroups:

- patients with sepsis versus those without sepsis.

### *Interventions*

- Oesophageal Doppler monitoring (ODM).

### *Comparator*

For both patient groups:

- no cardiac monitoring
- PACs
- pulse contour analysis monitoring
- lithium dilution cardiac monitors (i.e. LiDCO monitor)
- thermodilution cardiac monitors (i.e. PiCCO monitor).

### *Outcomes*

There is no generally recognised gold standard for the measurement of cardiac output, and for this reason we are focusing on patient-related outcomes rather than diagnostic performance.

If evidence permits, the main outcome measures to be assessed will be:

- 30-day mortality
- hospital mortality
- longer term mortality
- overall length of hospital stay
- overall length of ICU stay
- overall length of stay in critical care facilities (ICU and HDU)
- days of organ support in ICU
- postoperative complications and morbidity such as cardiac events and organ system failures
- quality of life in year after surgery.

### *Search strategy*

Reviews of ODM exist but these reviews are not systematic. In addition, they focus on diagnostic performance rather than on the impact on clinical management and patient-centred outcomes. Such comparisons may be misleading as PACs cannot be considered to be a gold standard. It is for this reason that our search strategy will focus on identifying RCTs that compare management based on ODM with management without monitoring or with an alternative method of monitoring. (Scoping searches indicate that there may be RCTs meeting our inclusion criteria; however, if when conducting the review no RCTs are found that meet our criteria then consideration will be given to including data from non-randomised designs.)

The search strategy will involve searches of electronic databases and relevant professional and manufacturers' websites.

Electronic searches will be conducted to identify reports of published and ongoing studies, including previous systematic reviews, on the effectiveness and cost-effectiveness of ODM. Searches will be carried out for the time period 1990 to the present, for full papers only. English language papers only will be considered eligible for inclusion; however, studies published in languages other than English will be noted. Databases to be searched are listed in *Table 16*. Preliminary MEDLINE search strategies to be used are given in Protocol Appendix 1 and will be adapted for use in the other databases.

Current research registers, including the National Research Register, Current Controlled Trials and Clinical Trials will be searched.

### *Inclusion criteria*

For the review of clinical effectiveness, only RCTs will be included. Data will be systematically assembled and quality will be assessed using criteria relevant to each type of outcome. Titles and abstracts will be examined for inclusion by one reviewer. Where there is uncertainty this will be discussed with a second reviewer and a consensus will be reached.

### *Exclusion criteria*

- Non-randomised studies
- Studies in which ODM is used to measure a study outcome rather than as a clinical monitor
- RCTs comparing ODM with other interventions not specified in Comparator, above

***TABLE 16*** *Databases to be searched*

| Clinical effectiveness | Cost-effectiveness |
|---|---|
| MEDLINE | MEDLINE |
| MEDLINE Extra | MEDLINE Extra |
| EMBASE | EMBASE |
| CINAHL | CINAHL |
| Science Citation Index | Science Citation Index |
| BIOSIS | Health Management Information Consortium (HMIC) |
| UK PubMed Central | UK PubMed Central |
| Cochrane Central Register of Controlled Trials (CENTRAL) | NHS Economic Evaluation Database (NHS EED) |
| Health Technology Assessment Database (HTA) | Health Technology Assessment Database |
| Cochrane Database of Systematic Reviews (CDSR) | |
| Database of Abstracts of Reviews of Effectiveness (DARE) | |

- Studies published in languages other than English
- Animal models
- Pre-clinical and biological studies
- Narrative reviews, editorials, opinions
- Reports published as meeting abstracts only.

### *Data extraction strategy*

All citations identified by the search strategy will be screened on the basis of the title and – where available – of the abstract. Full text copies of all potentially relevant reports will be obtained. One reviewer will assess studies for inclusion and extract data using a standard data extraction form (see Protocol Appendix 2). Any uncertainty will be resolved by discussion with a second reviewer and any disagreements will be resolved by arbitration by a third party. Information will be recorded on year of publication; source of funding; study design; methods prior to randomisation (e.g. stratification); method of randomisation; concealment of allocation; blinding procedures; number and characteristics of participants; duration of interventions; choice of outcome measures; and length of follow-up. Care will be taken to avoid double counting due to multiple reports of the same data set. The reviewer will not be blinded to authors, institutions or publications. Where there is insufficient information in the published report, no attempt will be made to contact the authors for clarification because of time constraints.

### *Quality assessment strategy*

The study quality of RCTs will be assessed using the Delphi criteria list (see Protocol Appendix 3), adapted from Verhagen and colleagues.[13]

### *Methods of analysis/synthesis*

For trials with multiple publications, only the most up-to-date or complete data for each outcome will be included. Where appropriate, meta-analysis will be employed to estimate a summary measure of effect on relevant outcomes based on intention-to-treat analyses. Dichotomous outcome data will be combined using the Mantel–Haenszel relative risk method and continuous outcomes will be combined using the inverse variance weighted mean difference method. The 95% confidence intervals and $p$-values will be calculated for the estimates of RR and WMD. The results will be reported using a fixed-effects model. Chi-squared tests and $I^2$ statistics will be used to explore statistical heterogeneity across studies. Possible reasons for heterogeneity will be explored using sensitivity analysis. Where there is no clear reason for heterogeneity, the implications will be explored using random-effects methods. Where a quantitative synthesis is considered to be inappropriate or not feasible, a narrative synthesis of results will be provided. If a lack of uniformity of the data is present in many studies, a qualitative review to look for consistency between studies will be performed. This will be supplemented, where appropriate, by investigation of the consistency in the direction of the results using the Sign test.[16]

Length of hospital stay will be defined as time from admission to discharge or death and length of ICU will be defined as time from admission to discharge from ICU or death in ICU. Length of stay data will only be interpreted in the light of the mortality data.

### *Systematic review of existing economic evaluations*

The cost-effectiveness of ODM will be addressed by conducting a systematic review of economic evaluations of ODM against potential relevant comparators and for the pertinent patient groups as described above. Searches for this will be adapted to those used for the systematic review of clinical effectiveness but tailored to find relevant economic evaluation studies. Non-English language studies will be excluded except where an NHS EED English language abstract is available. In this situation the NHS EED abstract will be used as the primary reference.

One reviewer will assess all abstracts for relevance and will ask for full papers to be obtained for those that appear to be potentially relevant. Studies that compare relevant alternatives in terms of their cost and effects will be included in the analysis. One economist will assess included studies using well-known guidelines for economic evaluation assessment.[30,54] These guidelines address all the important issues that should be reported when conducting an economic evaluation in health care. No attempt will be made to synthesise quantitatively the identified primary studies.

The following data will be extracted for each included study:

1. Study characteristics (research question; study design; comparison; setting; basis of costing)
2. Characteristics of the study population (numbers receiving or randomised to each intervention; other systematic differences in clinical management; inclusion/exclusion criteria; dates to which data on effectiveness and costs are related)

3. Duration of follow-up for both effectiveness and costs
4. Results (summary of effectiveness and costs [point estimate and if reported range or standard deviation (SD)]; summary of cost-effectiveness/utility (point estimate and if reported range or SD); sensitivity analysis)
5. Conclusions as reported by the authors of the study.

Data from all included studies will be summarised and appraised in order to identify common results, variations and weaknesses between studies. If a study does not report ICERs but provides sufficient data then, where possible, the data will be reanalysed to provide estimates of ICERs. Particular attention will be given to relevant subgroup analyses within the included studies. These data will then be interpreted alongside the results of the systematic review of effectiveness to aid assessment of the relative efficiency.

**Potential additional work**
A health economist will explore the possibility of developing a simple health economic model to further address cost-effectiveness of ODM. The structure of such a model would be informed by advice from our clinical collaborators and would be parameterised using the best available UK-relevant data. However, owing to the very short duration of the present TAR, we cannot anticipate that a full new economic evaluation will be conducted.

## Expertise in this TAR team

The TAR team is experienced in conducting reviews of diagnostic and therapeutic interventions in both the clinical and technical aspects required to address the commissioning brief. The Lead reviewer and almost all the other members of the review team have all been involved in a considerable number of similar studies. Local clinical expertise will be provided by Dr Brian Cuthbertson, Senior Lecturer in critical care and Dr Gordon Houston, Specialist Registrar in anaesthetics. Dr Cuthbertson is also an experienced health services researcher and has previously worked on NCCHTA-commissioned Health Technology Assessments.

### *TAR Centre*
The Aberdeen Assessment Group has a track record of producing this type of focused report, while adhering to tight timescales for various policy customers such as the National Institute for Health and Clinical Excellence, the National Screening Committee and the NHS R&D HTA Programme.

In the last 12 months several similar studies have been completed. These include reviews that investigate:

- minimally invasive procedures for benign prostatic enlargement
- screening for open-angle glaucoma
- detection and treatment of *Staphylococcus aureus* infection for patients on peritoneal dialysis for end-stage renal disease
- minimally invasive total hip replacement.

### *Team members' contributions*
Luke Vale, Senior Research Fellow, will be technical lead on this project and will be responsible for the day-to-day running of the review as well as supervision of the economic evaluation and review of effectiveness. Graham Mowatt, Research Fellow, will undertake the systematic review of effectiveness and Rodolfo Hernández, Research Fellow, will conduct the systematic review of economic evaluations and investigate the scope for a simple modelling exercise. Adrian Grant, Professor of Health Services Research, will provide additional supervision, methodological advice and comments on drafts of the review. Cynthia Fraser, Information Officer, will develop and run the search strategies and will be responsible for obtaining papers and reference management. Brian Cuthbertson, Clinical Senior Lecturer, and Gordon Houston, Specialist Registrar, will provide clinical support and advice as well as assisting with the review of effectiveness.

Contact details for clinical experts:

Dr Brian Cuthbertson MB ChB FRCA MD
Clinical Senior Lecturer
University of Aberdeen
Honorary Consultant Anaesthetist
NHS Grampian
Health Services Research Unit
Health Sciences Building
Foresterhill
Aberdeen AB25 2ZD

Dr Gordon Houston MB ChB FRCA
Specialist Registrar
Department of Anaesthetics
Aberdeen Royal Infirmary
Foresterhill
Aberdeen AB25 2ZN

## Competing interests of authors

None of the researchers involved in this review have any competing interests. Neither the Health Services Research Unit nor the Health Economics Research Unit receives any funding from any of the manufacturers of the technologies to be assessed.

## Timetable/milestones

Final protocol: 16 March 2007.

Draft final report: To be agreed.

## Appendices

***Protocol Appendix 1: Draft search strategy***

**MEDLINE strategy to identify randomised controlled trials**

Assessing clinical effectiveness:

1. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. cardioQ.tw.
4. teco.tw.
5. Echocardiography, Transesophageal/
6. or/1–5
7. exp echocardiography, doppler/
8. ultrasonography, doppler/
9. or/7–8
10. (oesophageal or esophageal or intra?esophageal or trans?esophageal).tw.
11. 9 and 10
12. 6 or 11
13. exp cardiac output/
14. cardiovascular physiologic processes/
15. blood circulation/
16. hemodynamic processes/
17. fluid therapy/
18. blood flow velocity/
19. hypovol?emia.tw.
20. cardiac output.tw.
21. (hemodynamic or haemodynamic).tw.
22. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
23. ((blood or flow) adj1 velocity).tw.
24. (fluid adj1 (load or preload or therap$or management)).tw.
25. or/13–24
26. 12 and 25
27. monitoring, physiologic/
28. intraoperative monitoring/
29. preoperative care/
30. perioperative care/
31. critical care/
32. intensive care/
33. ((intensive or critical) adj care).tw.
34. ICU.tw.
35. (surgery or surgical).tw.
36. (optimis$or optimiz$).tw.
37. (preoptimis$or preoptimiz$).tw.
38. (super normalis$or supernormalis$).tw.
39. (super normaliz$or supernormaliz$).tw.
40. monitor$.tw.
41. or/27–40
42. 26 and 41
43. clinical trial.pt.
44. randomi?ed.ab.
45. randomly.ab.
46. trial.ab.
47. groups.ab.
48. or/43–47
49. 42 and 48
50. limit 49 to humans
51. limit 50 to yr="1990 – 2007"

**MEDLINE strategy to identify studies**

Assessing cost-effectiveness:

1. 1 ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. cardioQ.tw.
4. teco.tw.
5. Echocardiography, Transesophageal/
6. or/1–6
7. exp echocardiography, doppler/
8. ultrasonography, doppler/
9. or/7–9
10. (oesophageal or esophageal or intra?esophageal or trans?esophageal).tw.
11. 9 and 10
12. 6 or 11
13. exp cardiac output/
14. cardiovascular physiologic processes/
15. blood circulation/
16. hemodynamic processes/
17. fluid therapy/
18. blood flow velocity/
19. hypovol?emia.tw.
20. cardiac output.tw.
21. (hemodynamic or haemodynamic).tw
22. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
23. ((blood or flow) adj1 velocity).tw.

24. (fluid adj1 (load or preload or therap$or management)).tw.
25. or/13–24
26. 12 and 25
27. monitoring, physiologic/
28. intraoperative monitoring/
29. preoperative care/
30. perioperative care/
31. critical care/
32. intensive care/
33. ((intensive or critical) adj care).tw.
34. ICU.tw.
35. (surgery or surgical).tw.
36. (optimis$or optimiz$).tw.
37. (preoptimis$or preoptimiz$).tw.
38. (super normalis$or supernormalis$).tw.
39. (super normaliz$or supernormaliz$).tw.
40. monitor$.tw.
41. or/27–40
42. 12 and 41
43. 26 or 42
44. exp "costs and cost analysis"/
45. economics/
46. exp economics,hospital/
47. exp economics,medical/
48. exp budgets/
49. exp models, economic/
50. exp decision theory/
51. ec.fs. use mesz
52. monte carlo method/
53. markov chains/
54. exp quality of life/
55. "Value of Life"/
56. cost of illness/
57. exp health status indicators/
58. cost$.ti.
59. (cost$adj2 (effective$or utilit$or benefit$or minimis$)).ab.
60. economics model$.tw
61. (economics$or pharmacoeconomic$or pharmo-economic$).ti.
62. (price$or pricing$).tw.
63. (financial or finance or finances or financed).tw.
64. (value adj2 (money or monetary)).tw.
65. quality adjusted life.tw.
66. disability adjusted life.tw.
67. (qaly? or qald? or qale? or qtime? or daly?).tw
68. (euroqol or euro qol or eq5d or eq 5d).tw.
69. (hql or hqol or h qol or hrqol or hr qol).tw.
70. (hye or hyes).tw.
71. (health adj3 (indicator? or status or utilit?)).tw.
72. markov$.tw.
73. monte carlo.tw.
74. (decision$adj2 (tree? or analy$or model$)).tw
75. or/44–74
76. 43 and 75

***Protocol Appendix 2: Data extraction form***
Clinical effectiveness of ODM in adults being managed in critical care or during major surgery

Reviewer: Data extraction date:

| **Study design** | |
|---|---|
| Study: | Country: |
| Aim of the study: | |
| ***Comparison:***<br>❑ ODM versus pulmonary artery catheterisation<br>❑ ODM versus pulse contour analysis monitoring:<br>❑ Lithium dilution cardiac monitors, i.e. LiDCO monitor<br>❑ Thermodilution cardiac monitors, i.e. PiCCO monitor<br>❑ ODM versus no cardiac monitoring<br>***Patient subgroups:***<br>❑ Patients with sepsis | |
| ***Setting:***<br>Patient recruitment date:<br>Length of follow up [mean/median (SD), range]:<br>Funding: government/private/manufacturer/other (specify):<br>Additional information on study design: | |
| **Participants** | |
| Inclusion criteria: | |
| Exclusion criteria: | |

| **Patient characteristics** | | | | |
|---|---|---|---|---|
| Specify | Intervention 1<br>ODM | Intervention 2 | Intervention 3 | Overall |
| Number of patients | | | | |
| Randomised | | | | |
| Lost to follow-up | | | | |
| Reason | | | | |
| Analysed | | | | |
| Age(years) [mean/median (SD), range] | | | | |
| Sex | M<br>F | M<br>F | M<br>F | M<br>F |
| Co-morbidities | | | | |
| Additional information on patients: | | | | |
| Indications for ODM | | | | |
| Intervention | | | | |
| Details of ODM intervention:<br><br>Practitioner experience:<br><br>Additional information: | | | | |
| Details of pulmonary artery catheterisation: | | | | |

| | | | |
|---|---|---|---|
| Details of pulse contour analysis monitoring: | | | |
| Details of standard care if no cardiac monitoring used: | | | |
| **Outcomes** | | | |
| Specify | Intervention 1<br>ODM | Intervention 2 | Intervention 3 |
| 30-day mortality [% (n/N)] | | | |
| Hospital mortality [% (n/N)] | | | |
| Longer term mortality<br>Length of follow up<br>[% (n/N)] | | | |
| Overall length of hospital stay [days, mean/median (SD), range] | | | |
| Overall length of stay in ICU [days, mean/median (SD), range] | | | |
| Overall length of stay in critical care facilities (ICU and HDU) [days, mean/median (SD), range] | | | |
| Days of organ support in ICU [mean/median (SD), range] | | | |
| Postoperative complications and morbidity [% (n/N)]<br>Cardiac events<br>Organ system failures<br>Other | | | |
| Quality of life in year after intervention<br>Instrument(s) | | | |

| | | | |
|---|---|---|---|
| Other effectiveness outcomes | | | |
| **Authors' conclusions** | | | |
| | | | |
| **Additional information** | | | |
| | | | |

***Protocol Appendix 3: Quality assessment form – RCTs (adapted from Verhagen et al 1998[13])***

Reviewer: Date:

| Criteria | Yes | No | Unclear | Comments |
|---|---|---|---|---|
| ***Was the sequence generation really random?*** | | | | |
| *Adequate approaches to sequence generation* | | | | |
| Computer-generated random tables | | | | |
| Random number tables | | | | |
| *Inadequate approaches to sequence generation* | | | | |
| Use of alternation, case record numbers, birth dates or week days | | | | |
| ***Was the treatment allocation concealed?*** | | | | |
| *Adequate approaches to concealment of randomisation* | | | | |
| Centralised or pharmacy-controlled randomisation | | | | |
| Serially-numbered identical containers | | | | |
| On-site computer-based system with a randomisation sequence that is not readable until allocation | | | | |
| Other approaches with robust methods to prevent foreknowledge of the allocation sequence to clinicians and patients | | | | |
| *Inadequate approaches to concealment of randomisation* | | | | |
| Use of alternation, case record numbers, birth dates or week days | | | | |
| Open random number lists | | | | |
| Serially-numbered envelopes (even sealed opaque envelopes can be subject to manipulation) | | | | |
| ***Were the groups similar at baseline regarding the most important prognostic indicators?*** | | | | |
| ***Were the eligibility criteria specified?*** | | | | |
| ***Were the groups treated in the same way apart from the monitoring tool used?*** | | | | |
| ***Was the outcome assessor blinded?*** | | | | |
| ***Was the care provider blinded?*** | | | | |
| ***Were the patients blinded?*** | | | | |
| ***Were the point estimates and measures of variability presented for the primary outcome measures?*** | | | | |
| ***Was the withdrawal/drop-out rate likely to cause bias?*** | | | | |
| ***Did the analyses include an intention-to-treat analysis?*** | | | | |
| ***Was the monitoring procedure undertaken by somebody experienced in performing the technique?*** | | | | |

# Appendix 2

# Aberdeen TAR group critique of the AHRQ report, using the Database of Abstracts of Reviews of Effectiveness (DARE) criteria


## Summary

This publication reported a well-conducted systematic review assessing oesophageal Doppler ultrasound-based cardiac output monitoring for real-time therapeutic management of hospitalised patients. Four key questions were addressed:

1. What types of devices/techniques are currently used to assess cardiac output?
2. Does therapeutic management based on oesophageal Doppler ultrasound-based cardiac output monitoring during *surgery* lead to improved patient outcomes (fewer complications and shorter hospital stay) compared with:
   i. Pulmonary artery catheter-based measurement of cardiac output via thermodilution?
   ii. Catheter-based measurement of central venous pressure (CVP)?
   iii. Conventional clinical assessment (physical examination, fluid input and output measurements)?
3. Does therapeutic management based on oesophageal Doppler ultrasound-based cardiac output monitoring during *hospitalisation* lead to improved patient outcomes (fewer complications and shorter hospital stay) compared with:
   i. Pulmonary artery catheter-based measurement of cardiac output via thermodilution?
   ii. Catheter-based measurement of central venous pressure (CVP)?
   iii. Conventional clinical assessment (physical examination, fluid input and output measurements)?
4. What complications, harms, and adverse events associated with oesophageal Doppler ultrasound-based monitoring have been reported?

Twenty-seven studies met the inclusion criteria for at least one key question. The ODM devices evaluated in the review included CardioQ (Deltex Medical Ltd., UK), HemoSonic 100 (Arrow International, USA) and TECO (Medicina Ltd., UK, but no longer commercially available). Earlier models of these devices were also included. The review focused on patient-orientated outcomes.

The authors' conclusions were:

Q1. Methods used to monitor cardiac output in patients during surgery or intensive care. These methods include thermodilution, dye dilution, lithium dilution, methods using the Fick principle, pulse contour methods, thoracic electrical bioimpedance, transoesophageal echocardiography, oesophageal Doppler monitoring and ultrasonic cardiac output monitoring.

Q2. Seven publications with 583 patients addressed this question. None of the studies compared ODM with thermodilution. Five studies were of ODM plus CVP monitoring plus conventional clinical assessment versus CVP monitoring plus conventional clinical assessment. Two studies were of ODM plus conventional clinical assessment versus conventional clinical assessment alone.

The addition of ODM for guided fluid replacement to a protocol using CVP monitoring plus conventional clinical assessment during surgery leads to a clinically significant reduction in the rate of major complications and total complications in surgical patients compared with CVP monitoring plus conventional clinical assessment. The strength of evidence supporting this finding is strong.

The addition of ODM to the protocol described above also reduces the length of hospital stay for surgical patients (clinical significance uncertain). The strength of evidence supporting this finding is strong.

Only one study compared ODM plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment. Because this was

one small study with non-informative effect sizes, no evidence-based conclusions were possible for any of the outcomes of interest.

The addition of ODM for guided fluid replacement to conventional clinical assessment during surgery leads to a clinically significant reduction in the length of hospital stay compared with that associated with conventional clinical assessment alone. The strength of evidence supporting this finding is weak.

The evidence was insufficient to allow conclusions to be reached concerning relative mortality rates for any of the comparisons in key question 2.

The conclusions for key question 2 apply only to patients undergoing surgical procedures with an expected substantial blood loss or fluid shifts requiring fluid replacement.

Q3. One study addressed this question, comparing ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment for optimisation of intravenous fluid replacement in patients admitted to intensive care following cardiac surgery. This was a single small study without a demonstrably large treatment effect on the outcomes of interest. Therefore, no conclusions could be drawn for this question.

Q4. Currently, no serious adverse events associated with oesophageal Doppler probes have been reported in the literature or in adverse event databases. The only minor events identified included two cases of incorrect probe placement in the left main bronchus, one case of incorrect placement in the trachea, a tube displacement during probe removal and an unspecified number of cases of minimal trauma in the buccal cavity during probe placement. Nineteen studies with a total of 654 patients specifically stated that oesophageal Doppler probes did not cause any complications. The number of patients represented in these studies is relatively small. However, the available evidence suggests that oesophageal Doppler probes are relatively low-risk devices, as reporting of even minor morbidity has been infrequent thus far.

## Authors' objective

The authors' objective was to provide a report to inform the US Centers for Medicare and Medicaid Services of the evidence regarding oesophageal Doppler ultrasound-based monitoring of cardiac output.

## Specific interventions included in the review

For key questions 2 and 3, ODM was compared with a standard of care, ideally catheter-based measurements of cardiac output or CVP, but also including other conventional clinical assessments.

The AHRQ report stated that transoesophageal echocardiography (TEE) with Doppler differs from ODM in that TEE requires more training to operate and is more expensive. TEE systems were beyond the scope of the AHRQ report.

## Participants included in the review

The participants were patients undergoing surgery (key question 2), or during hospitalisation (key question 3) or either (key question 4).

The authors noted that inclusion/exclusion criteria and patient characteristics described in studies of cardiac output monitoring suggested that the target population was relatively high-risk patients undergoing major surgical procedures such as bowel resection, hip fracture repair or cardiac surgery, with a significant anticipated blood loss, or patients in intensive care. The authors stated that cardiac output-guided fluid replacement is not generally considered for low-risk patients having ambulatory surgery.

The participant inclusion criterion did not apply to key question 1, which was concerned with the types of device used to measure cardiac output.

## Outcomes assessed in the review

For key questions 2 and 3, mortality, major complications, total complications and length of hospital stay were the main outcome measures. For key question 4, all outcomes reported complications that may be related to use of oesophageal Doppler ultrasound devices. The report evaluated only patient-orientated outcomes.

## Study designs of evaluations included in the review

Studies were included if they were English language, addressed one of the four key questions, were published as full journal articles and, for

controlled studies, enrolled 10 or more patients per treatment group. If the same study was reported in multiple publications, only the most recent publication was included.

In addition:

For key question 1 clinical guidelines, review articles and US Food and Drug Administration (FDA) approvals were used to identify other methods of cardiac output monitoring.

For key questions 2 and 3, studies had to involve a parallel group design with a head-to-head comparison of ODM with standard-of-care monitoring in separate patients. Within a given trial, patients in both groups must have received comparable surgery (key question 2) or must have had comparable diagnoses (key question 3). Studies performing a mixed analysis of surgical and non-surgical patients were excluded, as such studies could not answer key question 2 or 3.

For key question 4, studies of any design (controlled trials, case series, case reports), the ECRI's Health Device Alerts database and other adverse event databases were examined for reports of complications, harms and adverse events. These sources could not be used to determine causality or to estimate frequency of adverse events, but were used to generate a list of adverse events possibly attributable to the technology.

## What sources were searched to identify primary studies?

The original search was to June 2006, followed by an updated search to September 2006.

### *Electronic database searches*

Seventeen external and internal databases were searched: MEDLINE (1966 to 11 September 2006), EMBASE (1974 to 11 September 2006), The Cochrane Database of Systematic Reviews (Issue 3, 2006), The Cochrane Database of Methodology Reviews (Issue 3, 2006), The Cochrane Central Register of Controlled Trials (Issue 3, 2006), Database of Abstracts of Reviews of Effectiveness (Issue 3, 2006), CINAHL (1982 to 11 September 2006), ECRI Health Devices Alerts (1977 to 7 June 2006), ECRI International Health Technology Assessment (inception to 7 June 2006), ECRI Library Catalog (inception to March 2006), Health Technology Assessment Database (inception to Issue 3, 2006), metaRegister of Controlled Trials (14 June 2006), PubMed (1 September 2006), NHS Economic Evaluation Database (inception to Issue 3, 2006), US Centers for Medicare & Medicaid Web site (inception to 19 June 2006), US Food and Drug Administration (adverse event reports) (1977 to 7 June 2006), US National Guideline Clearinghouse (14 June 2006).

### *Hand searches of journal and non-journal literature*

Over 1600 journals and supplements maintained in the ECRI's collections were routinely reviewed. Non-journal publications and conference proceedings from professional organisations, private agencies and government agencies were also screened. Other mechanisms used to retrieve additional relevant information included review of bibliographies/reference lists from peer-reviewed and grey literature.

Only published, peer-reviewed, English language full text articles were considered for inclusion in the review.

## Validity assessment

Quality assessment of studies included for key questions 2 and 2 was undertaken using an ECRI 25-question tool. Questions were worded so that study design aspects that provided evidence with good internal validity resulted in 'Yes' answers, design aspects that created potential for bias resulted in 'No' answers and design aspects that were inadequately described resulted in an answer of 'NR' (not reported). The tool considered the comparability of the groups at baseline, blinding, outcome measurement, treatment and investigator bias. These items were used to compute a summary score, where 10 indicated an ideal study and 0 indicated a study of the poorest possible quality. Studies that scored $< 5$ were considered unacceptable quality, those scoring $> 5$ but $\leq 6.7$ were considered low quality, those that scored $> 6.7$ but $\leq 8.4$ were considered moderate quality and studies scoring $\geq 8.5$ were considered high quality.

The number of reviewers conducting the quality assessment was not stated.

The information used for key question 1 was not formally evaluated. The quality of the evidence for key question 4 was not formally evaluated as the intent of the question was simply to list reported harms of oesophageal Doppler ultrasound probes from any available data sources.

## How were decisions on the relevance of primary studies made?

From 317 potentially relevant citations identified, 75 full text articles were retrieved. Each article was read to determine whether it met a set of general and question-specific a priori inclusion criteria. Twenty-seven of the retrieved articles met the inclusion criteria for at least one key question, and four addressed more than one key question. Seven included studies addressed key question 2, one addressed key question 3 and 23 addressed key question 4. The authors stated that as key question 1 was a survey of current techniques rather than an evaluation of evidence the papers addressing it were not included in the above figures. The number of reviewers who selected reports for inclusion was not stated.

## How were the data extracted from the primary studies?

Data were extracted that described patient inclusion/exclusion criteria, design details (prospective, blinding status, etc), information on enrolled patients (demographics, underlying risk, etc), and study results. When study authors did not report dichotomous data as percentages, these were computed. Only outcome data relevant to the key questions in the report were extracted. The number of reviewers who extracted data was not stated.

## Number of studies included

As key question 1 required a summary of the technologies used to measure cardiac output, it was derived primarily from review articles written by experts in the field and was not truly evidence based, and the number of studies providing information for this question was not reported. Seven studies ($n = 583$) were included for key question 2, one study ($n = 174$) was included for key question 3 and 23 studies were included for key question 4. Because the intent of key question 4 was simply to list reported harms of oesophageal Doppler ultrasound probes from any available data source, details of study participants were not reported.

## How were the studies combined?

Individual study effect sizes were calculated from dichotomous data using the log odds ratio (summary log odds ratios were converted to odds ratios in the text and conclusion statements). If there were no events in one of the study groups, the Peto log odds and odds ratios were used. Effect sizes for continuous data were calculated in the original metric.

In some instances, certain studies presented data for a continuous outcome (length of hospital stay) in a form that did not allow calculation of a precise effect size. Whereas accurate calculation of an effect requires means and standard deviations or 95% confidence intervals, some studies report length of stay as medians and ranges. The authors based their primary analysis of length of stay on medians and ranges when available, arguing that in some studies the mean may be considerably skewed by outliers. Imputation methods were used to estimate effect sizes from the median, range and sample size when possible. If studies reported medians and IQRs, the distance between the median and the 25th percentile was assumed to be 0.67 standard deviations. If medians were not available, effect sizes were calculated from means and standard deviations.

Whenever relevant data from three or more studies were available and combining them was considered appropriate, the results were summarised using meta-analysis. The available data were first tested to determine whether the results of the studies included in the meta-analysis differed from one another by more than would be expected by chance (heterogeneity testing) using the $I^2$ statistic ($I^2 \geq 50\%$ indicating notable unexplained inconsistency). If study results did not differ in this manner, the study results were pooled in a fixed-effects model to obtain a summary estimate. Random-effects meta-analysis was performed to enable a qualitative conclusion if $I^2 \geq 50\%$ or if fewer than 80% of studies reported the outcome of interest or had calculable effect sizes.

## How were the differences between studies investigated?

Having obtained a summary estimate of the results, the robustness of the findings was tested by means of sensitivity analysis. Each study was removed separately to determine whether any one study had a substantial influence on the meta-analytic findings. The systematic addition of each study (cumulative meta-analysis) was also performed to determine the study's effect on the summary result. Studies were added in order, beginning with the highest-weighted study and ending with the lowest-weighted study (studies were also added in reverse order). These sensitivity analyses were used for

testing both quantitative and qualitative robustness. As a further test of qualitative robustness, summary effects were recalculated in a different metric (Cohen's h in place of the log odds ratio, Hedges' g in place of the weighted mean difference) to see if this overturned the qualitative conclusions. Because of the assumptions used in meta-analysis of length of stay, additional sensitivity analyses were undertaken on this outcome.

In instances where the evidence base consisted of two studies and the median quality of the studies was high, the studies were combined in a meta-analysis in an attempt to reach a qualitative (but not quantitative) conclusion.

## Results of the review

### *Key question 1 (What types of devices/techniques are currently used to assess cardiac output?)*

Methods used to monitor cardiac output in patients during surgery or intensive care included thermodilution, dye dilution, lithium dilution, methods using the Fick principle, pulse contour methods, thoracic electrical bioimpedance, transoesophageal echocardiography, ultrasonic cardiac output monitoring and ODM.

### *Key question 2 (Does therapeutic management based on oesophageal Doppler ultrasound-based cardiac output monitoring during surgery lead to improved patient outcomes?)*

Seven RCTs[17,18,20–24] involving 583 patients addressed this question, reporting three comparisons. None of the studies compared ODM with thermodilution. Although all of the studies except that by Venn and colleagues[23] reported placing Doppler probes in the control group patients during surgery. Doppler monitoring was not used in the fluid maintenance protocol in control patients.

Six of the seven studies used the CardioQ ODM system or an earlier model of this system while Conway and colleagues[17] used the TECO system. The types of surgery performed included elective bowel surgery,[17,21,24] hip fracture repair surgery,[22,23] elective cardiac surgery[20] and elective general, urological or gynaecological surgery.[18]

The five studies comparing ODM plus CVP monitoring plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment had a median quality score of 8.9 (range 8.1–9.7) on the ECRI quality scale, resulting in a quality rating of high for this evidence base. The two studies comparing ODM plus conventional clinical assessment with conventional clinical assessment had a median quality score of 9.0 (range 8.9–9.0), also resulting in a quality rating of high. One of these studies[23] also compared ODM plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment.

#### ODM plus CVP plus conventional assessment versus CVP plus conventional assessment

Five studies involving 453 patients reported this comparison. The types of surgery performed included elective bowel surgery,[17,21,24] elective cardiac surgery[20] and elective general, urological or gynaecological surgery.[18]

##### *Mortality*

No study reported any deaths during surgery. Three studies[17,20,21] reported one death each in the control group within 30 days following surgery, and one study[24] reported a death in the control group within 60 days following surgery, but the between-group differences were not statistically significant.

##### *Major complications*

Three of five studies reported major complications,[17,20,21] generally defined as life threatening or requiring intensive or high-dependency care. All studies showed a statistically significant reduction in major complications in the Doppler-monitored group. Because each study reported no major complications in the ODM group, the Peto method was used for calculating odds ratios. The Peto ORs (95% CIs) for the three studies were −2.08 (−3.72 to −0.44),[21] −2.19 (−4.01 to −0.37)[17] and −2.19 (−3.86 to −0.51).[20] Although a Peto random-effects meta-analysis was undertaken, an overall pooled estimate was not presented as only three of the five studies presented separate data on major complications. However, the 95% CI was 0.04–0.31, indicating statistically significantly fewer major complications associated with ODM.

##### *Total complications*

Four of five studies reported total complications.[17,18,21,24] Two of these four studies showed a statistically significant difference indicating fewer total complications in the Doppler-monitored group, with OR (95% CI) 0.23 (0.10–0.54)[18] and 0.41 (0.20–0.84),[24] while the remaining two studies also showed fewer complications but the difference was not

significant, with OR 0.44 (0.13–1.54)[17] and OR 0.47 (0.20–1.07).[21] Gan and colleagues[18] reported the total number of complications rather than the number of patients with complications. Although a random-effects meta-analysis was undertaken, an overall pooled estimate was not presented as the studies reported complications somewhat differently (patients versus events). However, the 95% CI was −1.43 to −0.57, indicating statistically significantly fewer total complications associated with ODM.

***Length of hospital stay***
All five studies reported this outcome. Four studies reported a statistically significant reduction in length of stay (based on either medians or means) associated with Doppler-monitored fluid replacement, with a median of 6 versus 7 days, $p = 0.03$,[18] 7 (IQR 3–35) versus 9 (IQR 4–45) days, $p = 0.005$,[21] 10 (IQR 5.75) versus 11.5 (IQR 4.75) days, $p = 0.03$,[24] and a mean of 6.4 (range 5–9) versus 10.1 (range 5– 48) days, $p = 0.01$.[20] The fifth study, by Conway and colleagues,[17] reported a median of 12 (range 7–103) days for the Doppler group versus 11 (range 7–30) days for the control group ($p$-value not reported). In this study, one patient in the Doppler group remained in hospital for 103 days, not because of complications but because a social/community placement could not be found. Although a random-effects meta-analysis was undertaken, an overall pooled estimate was not presented on the grounds that three of the five studies reporting this outcome did not present data that allowed a precise effect size to be calculated. However, the 95% CI was −2.21 to −0.57, indicating a statistically significantly shorter length of hospital stay associated with ODM.

**ODM plus conventional assessment versus CVP plus conventional assessment**
One study[23] compared ODM plus conventional assessment ($n = 30$) with CVP monitoring plus conventional assessment ($n = 31$) [and also with conventional assessment alone ($n = 29$), see below] in patients undergoing surgery for hip fracture repair.

***Mortality***
There were fewer deaths in the ODM group (3/30 versus 6/31, $p = 0.30$), although the difference was not statistically significant.

***Major complications***
Venn and colleagues[23] did not report major complications separately from total complications.

***Total complications***
There were 46.7% (14/30) complications in the ODM plus conventional assessment group compared with 51.6% (16/31) in the CVP monitoring plus conventional assessment group. The difference in the rate of total complications (comprising mostly infections and cardiovascular events) favoured the ODM group without being statistically significant (OR 0.82, 95% CI 0.30–2.25). In terms of the number of patients experiencing complications, 33.3% (10/30) patients in the ODM group experienced complications compared with 45.2% (14/31) patients in the CVP monitoring group. The difference in the number of patients experiencing complications also favoured the ODM group, but again without reaching statistical significance (OR 0.61, 95% CI 0.21–1.72).

***Length of hospital stay***
The difference in the mean length of hospital stay between the ODM and CVP monitoring group was not statistically significant (13.5 versus 13.3 days, respectively, $p = 0.96$).

**ODM plus conventional assessment versus conventional assessment**
Two studies involving 130 patients undergoing surgery for hip fracture repair reported this comparison.[22,23]

***Mortality***
No deaths occurred during surgery in either study. Venn and colleagues[23] reported three (3/30) deaths in the ODM group and two (2/29) in the control group within 30 days following surgery, while Sinclair and colleagues[22] reported no (0/20) deaths in the ODM group and one (1/20) in the control group during this period. Sinclair and colleagues[22] reported a further two deaths (one in the ODM group and one in the control group) after this period and within 3 months following surgery. In terms of total mortality rates, neither study showed a statistically significant difference between the two treatment groups.

***Major complications***
The study by Sinclair and colleagues[22] did not report complications and the study by Venn and colleagues[23] did not report major complications separately from total complications.

***Total complications***
Only Venn and colleagues[23] reported total complications. The ODM group experienced statistically significantly fewer complications (46.7%, 14/30) than the control group (79.3%,

23/29) (OR 0.23, 95% CI 0.07–0.72). However, in terms of the number of patients experiencing complications the difference between the ODM group (33.3%, 10/30) and the control group (55.2%, 16/29) was not statistically significant (OR 0.41, 95% CI 0.14–1.16).

***Length of hospital stay***
Both studies reported a shorter length of stay for the ODM group. Sinclair and colleagues[22] reported a statistically significantly shorter length of stay for the ODM group compared with the control group, with a median of 11 (range 3–23) days versus 20 (range 5–220) days, $p < 0.05$. In the study by Venn and colleagues,[23] although the ODM group experienced a shorter length of stay (mean 13.5 days, 95% CI 10.9–17.5) compared with the control group (mean 17.5 days, 95% CI 13.9–24.4) the difference was not statistically significant ($p = 0.31$). In a random-effects meta-analysis the pooled estimate was statistically significant in favour of patients receiving ODM (OR −6.76, 95% CI −1.83 to −1.68).

***Key question 3 (Does therapeutic management based on oesophageal Doppler ultrasound-based cardiac output monitoring during hospitalisation lead to improved patient outcomes?)***
One study[19] addressed this question, comparing ODM (CardioQ system) plus CVP monitoring plus conventional assessment with CVP monitoring plus conventional assessment in 174 patients admitted to cardiac intensive care following cardiac surgery. The study achieved a quality score of 8.5 on the ECRI quality scale, resulting in a quality rating of high.

**ODM plus CVP plus conventional assessment versus CVP plus conventional assessment**
***Mortality***
There were more deaths in the ODM group (4/89 versus 2/85) although the difference was not statistically significant ($p = 0.43$).

***Major complications***
Although McKendry and colleagues[19] stated that there was a trend towards fewer major postoperative complications and deaths in the ODM group, the authors did not report major complications separately from total complications.

***Total complications***
Although fewer patients in the ODM group (19.1%, 17/89) experienced complications compared with the control group (30.6%, 26/85), the difference was not statistically significant ($p = 0.08$).

***Length of hospital stay***
There was a statistically significantly shorter median length of stay in the ODM group (7 days, range not reported) compared with the control group (9 days), $p = 0.02$. The mean length of stay was also shorter in the ODM group (11.4 days) compared with the control group (13.9 days), $p$-value not reported.

***Key question 4 (What complications, harms and adverse events associated with oesophageal Doppler ultrasound monitoring have been reported?)***
Twenty-three studies addressed this question, including four RCTs,[17,21–23] 18 case series[7,10,11,34–48] and one article containing two case reports.[49] Because the intention was just to generate a list of all reported harms of oesophageal Doppler ultrasound probes, these studies were not assessed for quality.

Nineteen studies (four RCTs and 15 case series) involving 654 patients specifically stated that oesophageal Doppler probes led to no complications in any of the patients included in the studies.

Three case series[11,39,42] and the article containing two case reports[49] reported complications, harms or adverse events associated with oesophageal Doppler probes. A case series by Iregui and colleagues[39] involving 106 critically ill patients reported accidental removal of an orogastric tube during oesophageal probe removal. A study by Moxon and colleagues[42] involving 13 patients reported incorrect placement of an oesophageal Doppler probe in one patient's trachea, although this did not cause any adverse effect. A study by Singer and colleagues[11] involving 60 patients reported occasional minimal trauma in the buccal cavity during placement of the oesophageal probe but did not state the number of patients who experienced this problem. Chandan and Hull[49] reported two case reports of incorrect placement of an oesophageal Doppler probe in the left main bronchus, which led to adverse symptoms (increasing airway resistance and oxygen requirement) in one of the patients.

The authors stated that a search of the FDA's Manufacturer and User Facility Device Experience (MAUDE) database identified one report of a mechanical problem with a CardioQ Doppler

probe. While a nurse was cleaning one of these probes with a tissue, the probe boot (distal end of the probe) separated from the rest of the probe body. However, this particular probe did not cause any complication in the patient.

## Was any cost information reported?

No.

## Authors' conclusions

### *Key question 1*

Several methods are currently used to monitor cardiac output in patients during surgery or intensive care. These methods include thermodilution, dye dilution, lithium dilution, methods using the Fick principle, pulse contour methods, thoracic electrical bioimpedance, transoesophageal echocardiography, ultrasonic cardiac output monitoring and ODM.

### *Key question 2*

The addition of ODM for guided fluid replacement to a protocol using CVP monitoring and conventional clinical assessment during surgery leads to a clinically significant reduction in the rate of major and total complications in surgical patients compared with CVP monitoring plus conventional clinical assessment alone. The strength of evidence supporting this conclusion is strong.

The addition of ODM to the protocol described above also reduces the length of hospital stay for surgical patients (clinical significance uncertain). The strength of evidence supporting this conclusion is strong.

Only one study compared ODM plus conventional clinical assessment with CVP monitoring plus conventional clinical assessment. Because this was one small study with non-informative effect sizes, no conclusions were possible for any of the outcomes of interest.

The addition of ODM for guided fluid replacement to conventional clinical assessment during surgery leads to a clinically significant reduction in the length of hospital stay compared with conventional clinical assessment alone. The strength of evidence supporting this conclusion is weak. Because only a single study reported total complications, no conclusion was possible concerning this outcome.

No conclusion could be drawn concerning relative mortality rates for any of the comparisons in key question 2.

The AHRQ report stated that the conclusions reached for key question 2 applied only to patients undergoing surgical procedures with an expected substantial blood loss or significant fluid compartment redistribution requiring fluid replacement.

### *Key question 3*

The evidence base contained only one small study that was insufficient to allow conclusions to be reached about the effectiveness of ODM in hospitalised patients in non-operative settings.

### *Key question 4*

Currently, no serious adverse events associated with ODM have been reported in the literature or the MAUDE database. The only minor events identified included two cases of incorrect probe placement in the left main bronchus, one case of incorrect placement in the trachea, a tube displacement during probe removal and an unspecified number of cases of minimal trauma in the buccal cavity during probe placement. Nineteen studies with a total of 654 patients specifically stated that oesophageal Doppler probes did not cause any complications. The number of patients represented in these studies is relatively small. However, the available evidence suggests that oesophageal Doppler probes are relatively low-risk devices, as reporting of even minor morbidity has been infrequent thus far.

## Commentary

This systematic review addressed four clearly stated questions, three of which (key questions 2–4) were clinically relevant, and appropriate inclusion criteria were specified. The search strategy used to identify studies was comprehensive in terms of the sources searched, although it was restricted to published, peer-reviewed, English language full text articles, which might have resulted in the omission of some relevant data. Relevant details of the included studies that addressed key questions 2 and 3 were reported clearly and in full. Fewer details were given of the included studies that addressed key question 4, and no details were given of the studies that addressed key question 1, but this was appropriate given the nature of the evidence being sought. The methods used to minimise the introduction of error or bias during

the review process were partly described; no details were given of the number of reviewers who selected reports for inclusion. The methods used to synthesise the data were clearly described and appropriate. In general, this was a well-conducted and clearly-reported study and the authors' conclusions followed on from the data presented.

## What are the implications of the review?

### *Implications for practice*

The authors did not state any implications for practice.

### *Implications for research*

The authors did not state any implications for future research.

## Other reviews of related interest

Bundgaard-Nielsen M, Holte K, Secher NH, Kehlet H. Monitoring of peri-operative fluid administration by individualized goal-directed therapy. *Acta Anaesthesiol Scand* 2007;**51**:331–40.

Dark PM, Singer M. The validity of trans-esophageal Doppler ultrasonography as a measure of cardiac output in critically ill adults. *Intensive Care Med* 2004;**30**(11)2060–6.

Laupland KB, Bands CJ. Utility of esophageal Doppler as a minimally invasive hemodynamic monitor: a review. *Can J Anesth* 2002;**49**(4):393–401.

Price JD, Sear JW, Venn RM. *Perioperative fluid volume optimization following proximal femoral fracture*. Cochrane Database of Systematic Reviews 2004, Issue 1. Art. No.: CD003004. DOI: 10.1002/14651858.CD003004.pub2.

# Appendix 3

## Search strategies

### Clinical effectiveness

Search strategies used to identify reports of clinical effectiveness of ODM

**MEDLINE (1990 to May week 3 2007), EMBASE (1990 to 2007 week 20), (MEDLINE In Process 23 May 2007))**
Ovid Multifile Search – URL: http://gateway.ovid.com/athens

1. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. Echocardiography, Transesophageal/
4. or/1–3
5. exp echocardiography, doppler/
6. doppler echocardiography/
7. doppler flowmeter/
8. ultrasonography, doppler/
9. or/5–8
10. (oesophageal or esophageal or intra?esophageal or trans?esophageal).tw.
11. 9 and 10
12. 4 or 11
13. exp cardiac output/
14. heart output/
15. cardiovascular physiologic processes/
16. cardiovascular function/
17. hemodynamic processes/
18. heart hemodynamics/
19. hemodynamic monitoring/
20. fluid therapy/
21. blood flow velocity/
22. hypovol?emia.tw.
23. cardiac output.tw.
24. (hemodynamic or haemodynamic).tw.
25. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
26. ((blood or flow) adj1 velocity).tw
27. (fluid adj1 (load or preload or therap$or management)).tw.
28. hemodynamic monitoring/
29. heart output monitoring/
30. monitoring, physiologic/
31. intraoperative monitoring/
32. monitor$.tw.
33. ((optimis$or optimiz$) adj1 fluid).tw
34. (preoptimis$or preoptimiz$).tw
35. (super normalis$or supernormalis$).tw.
36. (super normaliz$or supernormaliz$).tw.
37. or/13–36
38. 12 and 37
39. cardioQ.tw,dv.
40. teco.tw,dv.
41. hemosonic.tw,dv.
42. dynemo.tw,dv.
43. odm.tw,dv.
44. or/38–43
45. preoperative care/
46. exp perioperative care/
47. critical care/
48. intensive care/
49. ((intensive or critical) adj3 care).tw.
50. (surgery or surgical).tw,hw
51. trauma.tw,hw
52. icu.tw.
53. or/45–52
54. 44 and 53
55. clinical trial.pt.
56. exp clinical trials/
57. randomi?ed.ab.
58. randomly.ab.
59. trial.ab.
60. groups.ab.
61. or/55–60
62. 54 and 61
63. animals/not humans/
64. nonhuman/
65. 62 not (63 or 64)
66. limit 65 to yr="1990–2007"
67. remove duplicates from 66

**CINAHL (1990 to May week 2 2007)**
Ovid Multifile Search – URL: http://gateway.ovid.com/athens

1. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. Echocardiography, Transesophageal/
4. or/1–3
5. exp echocardiography, doppler/

6. doppler echocardiography/
7. ultrasonography, doppler/
8. or/5–7
9. (oesophageal or esophageal or intra?esophageal or trans?esophageal).tw.
10. 8 and 9
11. 4 or 10
12. exp cardiac output/
13. fluid therapy/
14. blood flow velocity/
15. hypovol?emia.tw
16. cardiac output.tw.
17. (hemodynamic or haemodynamic).tw.
18. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
19. ((blood or flow) adj1 velocity).tw.
20. (fluid adj1 (load or preload or therap$or management)).tw.
21. monitoring, physiologic/
22. intraoperative monitoring/
23. monitor$.tw.
24. ((optimis$or optimiz$) adj1 fluid).tw.
25. (preoptimis$or preoptimiz$).tw.
26. (super normalis$or supernormalis$).tw.
27. (super normaliz$or supernormaliz$).tw.
28. or/12–27
29. 11 and 28
30. cardioQ.tw,dv
31. teco.tw,dv.
32. hemosonic.tw,dv
33. dynemo.tw,dv
34. odm.tw,dv
35. or/29–34
36. clinical trial.pt.
37. exp clinical trials/
38. randomi?ed.ab.
39. randomly.ab.
40. trial.ab.
41. groups.ab.
42. or/36–41
43. 35 and 42

**Science Citation Index**
**(1990 to 20 May 2007)**
***BIOSIS (1990 to17 May 2007)***
ISI Web of Knowledge – URL: http://wok.mimas.ac.uk/

#1. TS=(oesophageal SAME (doppler or ultason*)
#2. TS=(esophageal SAME (doppler or ultason*))
#3. TS=(intraoesophageal or intraesophageal or intra) SAME (doppler or ultason*)
#4. TS=(transoesophageal or transesophageal or trans) SAME (doppler or ultason*))
#5. #1 or #2 or #3 or #4
#6. TS=(hemodynamic or haemodynamic)
#7. TS=((stroke or circulatory or intravascular or fluid or plasma) SAME volume)
#8. TS=(fluid SAME (load or preload or therap* or management))
#9. TS=((blood or flow) SAME velocity)
#10. TS=heart output
#11. TS=cardiac output
#12. TS=(hypovolemia or hypovolaemia)
#13. TS=(fluid SAME (optimis* or optimiz*))
#14. TS=(preoptimis* or preoptimiz*)
#15. #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16. #5 and #15
#17. TS=(cardioq or teco or hemosonic or dynemo or odm)
#18. MQ=esophageal doppler monitor
#19. #18 or #19 or #20
#20. TS=surgical
#21. TS=surgery
#22. TS=icu
#23. TS=perioperative
#24. TS=preoperative
#25. TS=(critical SAME (care or illness))
#26. TS=(intensive SAME care)
#27. #22 or #23 or #24 or #25 or #26 or #27 or #28
#28. #21 and #29
#29. TS=randomized
#30. TS=randomised
#31. TS=trial*
#32. TS=(random or randomly)
#33. #31 or #32 or #33 or #34
#34. #21 and #35

**Cochrane Library (Issue 2, 2007)**
URL: http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/HOME

#1. (oesophageal NEAR/5 (doppler or ultrason*)) or (esophageal NEAR/5 (doppler or ultrason*)) or (intra?esophageal NEAR/5 (doppler or ultrason*)) or (trans?esophageal NEAR/5 (doppler or ultrason*))
#2. MeSH descriptor Echocardiography, Transesophageal, this term only
#3. (#1 OR #2)
#4. MeSH descriptor Echocardiography, Doppler explode all trees
#5. MeSH descriptor Ultrasonography, Doppler explode all trees
#6. (oesophageal) or (esophageal) or (intra?esophageal) or (trans?esophageal)
#7. ((#4 OR #5) AND #6)

#8. (#3 OR #7)
#9. MeSH descriptor Cardiac Output explode all trees
#10. MeSH descriptor Hemodynamic Processes, this term only
#11. MeSH descriptor Cardiovascular Physiologic Processes, this term only
#12. MeSH descriptor Fluid Therapy, this term only
#13. MeSH descriptor Blood Flow Velocity, this term only
#14. (hypovol?emia) or (cardiac output) or (hemodynamic) or (haemodynamic)
#15. (stroke next volume) or (circulatory next volume) or (intravascular next volume) or (fluid next volume) or (plasma next volume)
#16. ((blood or flow) near/1 velocity)
#17. (fluid near/1 (load or preload or therap* or management))
#18. MeSH descriptor Monitoring, Physiologic, this term only
#19. MeSH descriptor Monitoring, Intraoperative, this term only
#20. (monitor*) or (preoptimis*) or (preoptimiz*) or (optimis* near/1
#21. fluid) or (optimiz* near/1 fluid)
#22. (#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR
#23. OR #19 OR #20)
#24. (#8 AND #21)
#25. (cardioq) or (teco) or (hemosonic) or (dynemo) or (odm)
#26. (#22 OR #23)
#27. (#24), from 1990 to 2007

**National Research Register (Issue 2, 2007)**
URL: www.update-software.com/National/

#1. ECHOCARDIOGRAPHY TRANSESOPHAGEAL single term (MeSH)
#2. (esophageal near doppler)
#3. (oesophageal near doppler)
#4. ECHOCARDIOGRAPHY DOPPLER explode tree 1
#5. ULTRASONOGRAPHY DOPPLER explode all trees (MeSH)
#6. (oesophageal or esophageal or intraesophageal or transesophageal)
#7. ((#4 or #5) and #6)
#8. (#1 or #2 or #3 or #7)
#9. (cardioq or teco or hemosonic or dynemo or odm)
#10. (#8 or #9)

**DARE and HTA Databases (May 2007)**
***NHS Centre for Reviews & Dissemination***
URL: www.crd.york.ac.uk/crdweb/

1. MeSH Echocardiography, Transesophageal
2. (Oesophageal AND (DOPPLER OR ULTRASON*))
3. (esophageal AND (DOPPLER OR ULTRASON*))
4. (intra AND esophageal AND (DOPPLER OR ULTRASON*))
5. (intra AND oesophageal AND (DOPPLER OR ULTRASON*))
6. (trans AND oesophageal AND (DOPPLER OR ULTRASON*))
7. (trans AND esophageal AND (DOPPLER OR ULTRASON*))
8. #8(transesophageal AND (DOPPLER OR ULTRASON*))
9. (intraesophageal AND (DOPPLER OR ULTRASON*))
10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

**Clinical Trials (May 2007)**
URL: http://clinicaltrials.gov/ct/gui/c/r

**Current Controlled Trials (May 2007)**
URL: www.controlled-trials.com/
(oesophageal or esophageal) and Doppler

## Cost-effectiveness and economic evaluations

***Search strategies used to identify reports of cost-effectiveness and economic evaluations of ODM***

**MEDLINE (1990 to June week 3 2007), EMBASE (1990 to week 26 2007), (MEDLINE in Process 29 June 2007)**

Ovid Multifile Search – URL: http://gateway.ovid.com/

1. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. Echocardiography, Transesophageal/
4. or/1–3
5. exp echocardiography, doppler/
6. doppler echocardiograph/
7. doppler flowmeter/

8. ultrasonography, doppler/
9. or/5–8
10. (oesophageal or esophageal or intra?esophageal or trans?esophageal).tw
11. 9 and 10
12. 4 or 11
13. exp cardiac output/
14. heart output/
15. cardiovascular physiologic processes/
16. cardiovascular function/
17. hemodynamic processes/
18. heart hemodynamics/
19. fluid therapy/
20. blood flow velocity/
21. hypovol?emia.tw.
22. cardiac output.tw.
23. (hemodynamic or haemodynamic).tw.
24. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
25. ((blood or flow) adj1 velocity).tw.
26. (fluid adj1 (load or preload or therap$or management)).tw.
27. hemodynamic monitoring/
28. heart output monitoring/
29. monitoring, physiologic/
30. intraoperative monitoring/
31. monitor$.tw.
32. ((optimis$or optimiz$) adj1 fluid).tw.
33. (preoptimis$or preoptimiz$).tw
34. (super normalis$or supernormalis$).tw.
35. (super normaliz$or supernormaliz$).tw
36. or/13–36
37. 12 and 37
38. cardioQ.tw,dv.
39. teco.tw,dv
40. hemosonic.tw,dv.
41. dynemo.tw,dv.
42. odm.tw,dv.
43. or/38–43
44. preoperative care/
45. exp perioperative care/
46. critical care/
47. intensive care/
48. critical illness/
49. ((intensive or critical) adj3 care).tw.
50. (surgery or surgical).tw,hw.
51. icu.tw.
52. or/45–52
53. 44 and 53
54. exp "costs and cost analysis"/
55. economics/
56. exp economics,hospital/
57. exp economics,medical/
58. economics,pharmaceutical/
59. exp budgets/
60. exp models, economic/
61. exp decision theory/
62. ec.fs. use mesz
63. cost of illness/
64. cost$.ti.
65. (cost$adj2 (effective$or utilit$or benefit$or minimis$)).ab
66. economics model$.tw
67. (economics$or pharmacoeconomic$or pharmo-economic$).ti.
68. (price$or pricing$).tw.
69. (financial or finance or finances or financed).tw.
70. (value adj2 (money or monetary)).tw.
71. or/55–71
72. 54 and 72
73. remove duplicates from 73

**Science Citation Index**
**(1990 to 1 July 2007)**
ISI Web of Knowledge – URL: http://wok.mimas.ac.uk/

#1. TS=(oesophageal SAME (doppler or ultason*)
#2. TS=(esophageal SAME (doppler or ultason*))
#3. TS=(intraoesophageal or intraesophageal or intra) SAME (doppler or ultason*)
#4. 932 TS=(transoesophageal or transesophageal or trans) SAME (doppler or ultason*))
#5. #1 or #2 or #3 or #4
#6. TS=(hemodynamic or haemodynamic)
#7. TS=((stroke or circulatory or intravascular or fluid or plasma) SAME volume)
#8. TS=(fluid SAME (optimis* or optimiz*))
#9. TS=(preoptimis* or preoptimiz*)
#10. TS=(hypovolemia or hypovolaemia)
#11. TS=heart output
#12. TS=cardiac output
#13. TS=(fluid SAME (load or preload or therap* or management))
#14. TS=((blood or flow) SAME velocity)
#15. #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16. TS=(cardioq or teco or hemosonic or dynemo or odm)
#17. (#5 and #15) or #16
#18. TS=economic*
#19. TS=cost*
#20. TS=(price* OR pricing*)
#21. TS=(financial or finance*)
#22. TS=(decision* SAME (tree* OR analy* or model*))
#23. TS=markov*
#24. TS=monte carlo
#25. TS=(health SAME (indicator* or status or utilit*))

#26. TS=quality of life
#27. TS=quality adjusted life
#28. TS=disability adjusted life
#29. TS=(qaly* or qald* or qale* or qtime* or daly*)
#30. TS=(euroqol* or euro qol* or eq5d or eq 5d)
#31. TS=(hql or hqol or h qol or hrqol or hr qol)
#32. TS=(hye or hyes)
#33. #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32
#34. #17 AND #33

**NHS EED (May 2007)**
URL: www.crd.york.ac.uk/crdweb/

#1. MeSH Echocardiography, Transesophageal
#2. (Oesophageal AND (DOPPLER OR ULTRASON*))
#3. (esophageal AND (DOPPLER OR ULTRASON*))
#4. (intra AND esophageal AND (DOPPLER OR ULTRASON*))
#5. (intra AND oesophageal AND (DOPPLER OR ULTRASON*))
#6. (trans AND oesophageal AND (DOPPLER OR ULTRASON*))
#7. (trans AND esophageal AND (DOPPLER OR ULTRASON*))
#8. (transesophageal AND (DOPPLER OR ULTRASON*))
#9. (intraesophageal AND (DOPPLER OR ULTRASON*))
#10. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9

**HMIC (1990 to May 2007)**
URL: http://gateway.ovid.com/

1. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 doppler).tw.
2. ((oesophageal or esophageal or intra?esophageal or trans?esophageal) adj5 ultrason$).tw.
3. 1 or 2
4. hypovol?emia.tw.
5. cardiac output.tw.
6. (hemodynamic or haemodynamic).tw. (125044)
7. ((stroke or circulatory or intravascular or fluid or plasma) adj volume).tw.
8. ((blood or flow) adj1 velocity).tw
9. (fluid adj1 (load or preload or therap$or management2 monitor$.tw.
10. ((optimis$or optimiz$) adj1 fluid).tw.
11. (preoptimis$or preoptimiz$).tw.
12. or/4–11
13. 3 and 12
14. cardioQ.tw
15. teco.tw
16. hemosonic.tw
17. dynemo.tw
18. odm.tw
19. or/13–18

***Websites searched for other evidence-based reports and background information***

Anaesthesia UK – URL: www.frca.co.uk/
Critical Care – URL: http://ccforum.com/home/
Deltex Medical – URL: www.deltexmedical.com/
Hemosonic – URL: www.hemosonic.com/
Intensive Care Society – URL: www.ics.ac.uk/index.asp
International Collaboration for Excellence in Critical Care Medicine – URL: http://ice-ccm.medtau.org/
Merck Manual: Patient Monitoring and Testing – URL: www.merck.com/mmpe/sec06/ch063/ch063b.html
TriP Database – URL: www.tripdatabase.com/index.html
Surgical Critical Care – URL: www.surgicalcriticalcare.net/

# Appendix 4

## ECRI quality assessment scale applied to the two additional studies

| Questions | Study | |
|---|---|---|
| | **Chytra 2007[25]** | **Dodd 2004[26]** |
| 1. Were patients randomly assigned to groups? | Yes | Yes |
| 2. Did the study employ stochastic randomisation? | No | NR |
| 3. Were any methods used to make the groups comparable – randomisation, matching, etc? | Yes | Yes |
| 4. Were patients assigned to groups based on factors other than patient or physician preference? | Yes | Yes |
| 5. Were the characteristics of the patients in different groups comparable? | Yes | Yes |
| 6. Did the patients in the different study groups have similar levels of performance on outcomes at baseline? | Yes | Yes |
| 7. Was the study prospectively planned? | Yes | Yes |
| 8. Did 85% or more of the patients complete the study? | Yes | Yes |
| 9. Was there a less than 16% difference in completion rates between the study's groups? | Yes | Yes |
| 10. Were all of the study's groups concurrently treated? | Yes | Yes |
| 11. Was compliance with treatment greater than or equal to 85% in both of the study's groups? | Yes | Yes |
| 12. Were all of the study's groups treated at the same centres? | Yes | Yes |
| 13. Were subjects blinded to treatment? | No | Yes |
| 14. Did the authors test and confirm that blinding of patients was maintained? | No | NR |
| 15. Was the treating physician blinded to group assignment? | No | Yes |
| 16. Were the outcome assessors blinded to group assignment? | No | Yes |
| 17. Was there concealment of allocation? | NR | NR |
| 18. Was the outcome of interest objective and was it objectively measured? | Yes | Yes |
| 19. Were the same methods used to measure outcomes in all of the study's groups? | Yes | Yes |
| 20. Was the instrument used to measure the outcome standard? | Yes | Yes |
| 21. Was the same treatment given to all of the patients enrolled in the experimental group? | Yes | Yes |
| 22. Was the same treatment given to all of the patients enrolled in the control group? | Yes | Yes |
| 23. Were the follow-up times in all of the study's relevant groups approximately equal? | Yes | Yes |
| 24. Was the funding for this study derived from a source that does not have a financial interest in its results? | NR | NR |
| 25. Were the authors' conclusions supported by the data in the results section? | Yes | Yes |
| Quality score | 7.4 | 8.8 |
| Quality rating | Moderate | High |

NR, not reported.
ECRI uses these 25 items to compute a summary score ranging from 0 to 10, where 10 indicates an ideal study and 0 indicates a study of the poorest quality. Individual item answers were converted to numeric scores by counting 1 for each 'Yes' answer, −1 for each 'No' answer and −0.5 for each 'NR' answer. The numeric scores for all 25 items were then added and 25 was added to the total; this number was then divided by 50 and multiplied by 10. These calculations yielded the 0–10 summary scale. Studies that scored $< 5$ were considered to be of unacceptable quality, those scoring $> 5$ but $\leq 6.7$ were considered to be of low quality, those that scored $> 6.7$ but $\leq 8.4$ were considered to be of moderate quality and those scoring $\geq 8.5$ were considered to be of high quality.

# Appendix 5

## ODM in critically ill and high-risk surgical patients: quality assessment checklist for systematic reviews

Assessor initials: GM

Study identifier: AHRQ 2007[6]
(Surname of first author and year of publication)

1. Were the search methods used to find evidence (primary studies) on the primary question(s) stated?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

Comments:

2. Was the search for evidence reasonably comprehensive?

| | |
|---|---|
| No | |
| Partially | ✓ |
| Yes | |

| **Following done:** | |
|---|---|
| Language restrictions | Yes |
| Hand searching | Yes |
| Reference lists | Yes |
| Authors contacted | Yes |

Comments: Only published, peer-reviewed, English language full text articles were considered for inclusion.

3. Were the criteria used for deciding which studies to include in the review reported?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

| **Author specifies:** | |
|---|---|
| Type of study | Yes |
| Participants | Yes |
| Intervention(s) | Yes |
| Outcome(s) | Yes |

Comments:

4. Was bias in the selection of articles avoided?

| | |
|---|---|
| No | |
| Partially | ✓ |
| Yes | |

| **Author specifies:** | |
|---|---|
| Explicit selection criteria used? | Yes |
| Independent screening of full text by at least two reviewers? | Not stated |

Comments: No information was given on the number of reviewers who screened full text articles.

5. Were the criteria used for assessing the validity of the studies that were reviewed reported?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

| **Author specifies:** | |
|---|---|
| Criteria used to assess methodological quality? | Yes |

Comments:

6. Was the validity of all of the studies referred to in the text assessed using appropriate criteria (either in selecting studies for inclusion or in analysing the studies that are cited)?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

| **Author specifies:** | |
|---|---|
| Assessments of included studies using explicit criteria reported? | Yes |

Comments:

7. Were the methods used to combine the findings of the relevant studies (to reach a conclusion) reported?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

| | **Author specifies:** | |
|---|---|---|
| Meta-analysis | Outcome of interest? | Yes |
| | Model used? | Yes |
| | Test for heterogeneity? | Yes |
| Qualitative | Why meta-analysis inappropriate? | Yes |
| | How then made sense of data? | Yes |
| Both | Sensitivity analysis? | Yes |

Comments:

8. Were the findings of the relevant studies combined appropriately relative to the primary question the review addresses?

| | |
|---|---|
| No | |
| Partially | ✓ |
| Yes | |

| | |
|---|---|
| Interventions homogeneous? | Yes |
| Outcome measures homogeneous? | Yes |
| Participants homogeneous? | No |
| How unit analysis errors were handled? | Not stated |
| Settings comparable? | Yes |

Comments: Although the types of surgery differed, they all involved procedures anticipating a major loss of blood or significant fluid shifts requiring fluid replacement.

9. Were the conclusions made by the author(s) supported by the data and/or the analysis reported in the review?

| | |
|---|---|
| No | |
| Partially | |
| Yes | ✓ |

| | |
|---|---|
| Conclusions consistent with results? | Yes |
| Conclusions do not go beyond the data? | Yes |
| No evidence not interpreted as no effect? | Yes |
| Strength of recommendations for practice consistent with level of evidence (uncertainty)? | Yes |
| Recommendations for research consistent with identified shortcomings? | Not stated |

Comments:

10. Overall, how would you rate the methodological quality of this review?

| Extensive bias | | Major bias | | Minor bias | | Minimal bias |
|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5✓ | 6 | 7 |

Comments:

# Appendix 6

## List of excluded full text papers


Axler O. Evaluation and management of shock. *Semin Respir Crit Care Med* 2006;**27**(3):230–40.

Colbert S, O'Hanlon DM, Duranteau J, Ecoffey C. Cardiac output during liver transplantation. *Can J Anaesth* 1998;**45**(2):133–8.

Collins S, Girard F, Boudreault D, Chouinard P, Normandin L, Couture P *et al*. Esophageal Doppler and thermodilution are not interchangeable for determination of cardiac output. *Can J Anaesth* 2005;**52**(9):978–85.

Ellis JE. Con: pulmonary artery catheters are not routinely indicated in patients undergoing elective abdominal aortic reconstruction. *J Cardiothorac Vasc Anesth* 1993;**7**(6):753–7.

Hadian M, Angus DC. Protocolized resuscitation with esophageal Doppler monitoring may improve outcome in post-cardiac surgery patients. *Crit Care* 2005;**9**(4):E7–8.

Isakow W, Schuster DP. Extravascular lung water measurements and hemodynamic monitoring in the critically ill: bedside alternatives to the pulmonary artery catheter. *Am J Physiol* 2006;**291**(6):L1118–31.

Krishnamurthy B, McMurray TJ, McClean E. The peri-operative use of the oesophageal Doppler monitor in patients undergoing coronary artery revascularisation. A comparison with the continuous cardiac output monitor. *Anaesthesia* 1997;**52**(7):624–9.

Levinson MM. Intraoperative monitoring during cardiac surgery: some observations. *Heart Surg Forum* 1999;**2**(2):111–14.

Li FH, Hao J, Xia JG Li HL, Fang H. Hemodynamic analysis of esophageal varices in patients with liver cirrhosis using color Doppler ultrasound. *World J Gastroenterol* 2005;**11**(29):4560–5.

McFall MR, Woods WG, Wakeling HG. The use of oesophageal Doppler cardiac output measurement to optimize fluid management during colorectal surgery. *Eur J Anaesthesiol* 2004;**21**(7):581–3.

Matthews P. Cardiac output measurement using the TECO1 oesophageal Doppler monitor. A comparison with thermodilution. *Int J Intensive Care* 1998;**5**(3):78–81.

Nakamura S. Hemodynamics of esophageal varices on three-dimensional endoscopic ultrasonography and indication of endoscopic variceal ligation. *Dig Endosc* 2003;**15**(4):289–97.

Rocen M, Prikryl P, Zenkner W, Machalova O, Vychodil P, Cvachovec K. Fluid therapy during anaesthesia: comparison of standard and extensive method of haemodynamic monitoring. *Anesteziol Intenz Med* 2004;**15**(4):181–5.

Salmenpera M, Aittomaki J. Cardiac output monitoring: need for improvement? *Acta Anaesthesiol Scand* 2003;**47**(4):375–7.

Sanders GM. Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal resection. *Br J Surg* 2006;**93**(12):1563.

Stawicki SP, Hoff WS, Cipolla J, DeQuevedo R. Use of non-invasive esophageal echo-Doppler system in the ICU: a practical experience. *J Trauma* 2005;**59**(2):506–7.

Turner MA. Doppler-based hemodynamic monitoring: a minimally invasive alternative. *AACN Clin Issues* 2003;**14**(2):220–31.

van der Hoeven J, Olsman J. Hemodynamic monitoring in the critically ill patient. *Neth J Med* 2000;**57**(3):71–3.

Walley KR. Comparison of transesophageal echocardiographic, Fick and thermodilution cardiac output in crtitically ill patients. *J Crit Care* 1996;**11**(3):109–16.

# Appendix 7

## Indices used to guide clinical intervention in trial protocols/algorithm

| Study | Stroke volume | FTc | Cardiac output | CVP | Mean arterial pressure | Control group management |
|---|---|---|---|---|---|---|
| Conway 2002[17] | ✓ | ✓ | ✓[a] | | | Conventional management |
| Gan 2002[18] | ✓ | ✓ | ✓ | | | Conventional management plus triggers for fluid bolus[b] |
| McKendry 2004[19] | ✓[c] | | | | ✓ | Conventional management that may include cardiac output monitoring |
| Mythen 1995[20] | ✓ | | | ✓ | | Conventional management |
| Noblett 2006[21] | ✓ | ✓ | | | | Conventional management |
| Sinclair 1997[22] | ✓ | ✓ | | | | Conventional management |
| Venn 2002[23] (CVP group) | | | | ✓ | | Conventional management aiming for heart rate and arterial pressure within 20% of pre-induction of anaesthesia baseline |
| Venn 2002[23] (ODM group) | ✓ | ✓ | | | | |
| Wakeling 2005[24] | ✓ | | | ✓ | | Targeted CVP 12–15 mmHg |
| Chytra 2007[25] | ✓ | ✓ | | | | Conventional management |
| Dodd 2004[26] | ✓ | ✓ | | | | Conventional management |

FTc, corrected flow time.
a If cardiac output, stroke volume and waveform shape suggest fluid overload or impaired cardiac function, the investigator alerted the anaesthetist, ceased blinding of Doppler results and advised on the use of inotropes or vasodilators.
b Urine output < 0.5ml/kg/hour, heart rate increased either by > 20% from baseline or to greater than 10 beats per minute, blood pressure decreased by > 20% from baseline or to less than 90 mmHg systolic pressure, or fall in CVP (if monitored) of > 20%.
c Stroke index used instead of stroke volume.

# Appendix 8

## Characteristics and results of the two additional studies

| Study and country | Study design and purpose | Participants | Intervention | Results |
|---|---|---|---|---|
| Chytra 2007[25]<br>Country: Czech Republic | Design: RCT<br>Purpose: to examine the effect of oesophageal Doppler-guided fluid management during the first 12 hours after ICU admission on blood lactate levels, organ dysfunction development, infectious complications and length of ICU and hospital stays in comparison with standard haemodynamic management in multiple-trauma patients<br>ECRI quality score rating: 7.4 (moderate) | Enrolled: 162<br>Age [mean (range)]:<br>ODM: 33 (26–57)<br>Control: 40 (26–50)<br>Sex:<br>ODM: M: 73; F: 7<br>Control: M: 70; F: 12<br>Inclusion criteria: ventilated patients with multiple trauma and estimated blood loss of more than 2000 ml admitted to the interdisciplinary ICU<br>Exclusion criteria: patients < 18 years old, patients with traumatic brain injury requiring treatment of intracranial hypertension, and those with relative contraindications to the use of the oesophageal Doppler probe, such as orofacial and oesophageal injury or other known oropharyngeal and oesophageal disease | Treatment intervention: ODM (HemoSonic 100) + CVP + conventional assessment<br>Control intervention: CVP + conventional assessment | Mortality (hospital):<br>ODM: 13/80 (16.3%)<br>Control: 18/82 (22.0%)<br>Major complications: NR<br>Total complications (infectious) during ICU stay:<br>ODM: 15/80 (18.8%)<br>Control: 28/82 (34.1%)<br>Length of ICU stay (days) [median (range)]:<br>ODM: 7 (6–11)<br>Control: 8.5 (6–16)<br>$p = 0.031$<br>Length of hospital stay (days) [median (range)]<br>ODM: 14 (8.3–21)<br>Control: 17.5 (11–29)<br>$p = 0.045$ |
| Dodd 2004[26]<br>Country: UK | Design: RCT<br>Purpose: to investigate the possible beneficial effects on postoperative oral intake and time to medical fitness for discharge of ODM<br>ECRI quality score rating: 8.8 (high) | Enrolled: 40<br>Age [mean (SD)]:<br>ODM: 76.3 (6.3)<br>Control: 76.3 (7.2)<br>Sex:<br>ODM: M: 11; F: 9<br>Control: M: 9; F: 11<br>Type of surgery: colorectal<br>Inclusion criteria: patients undergoing elective major lower gastrointestinal surgery, age ≥ 65 years, ASA classification I–III<br>Exclusion criteria: NR | Treatment intervention: ODM (CardioQ) + conventional assessment<br>Control intervention: conventional assessment | Mortality (hospital):<br>ODM: 1/20 (5%)<br>Control: 2/20 (10%)<br>Major complications: NR<br>Total complications: NR<br>Length of stay in HDU [median (range)]:<br>ODM: 3 (2–10), $n = 7$<br>Control: 2 (2–10), $n = 5$<br>Length of hospital stay, reported as time to medically fit for discharge (days) [median (range)]:<br>ODM: 8 (5–34)<br>Control: 9 (5–27) |

ASA, American Society of Anesthesiologists; ECRI, Emergency Care Research Institute; HDU, high dependency unit; ICU, intensive care unit; NR, not reported.

# Appendix 9

## List of potentially relevant studies identified from a search of the National Research Register

| Study | Location | Title | Start and end dates | Notes |
|---|---|---|---|---|
| Cholley[a] | Hopital Lariboisière, Paris, France | Stroke volume optimisation in patients with hip fracture | April 2007–April 2010 | Contacted – study protocol provided |
| Dorman (Dodd)[b] | Poole Hospital, UK | Oesophageal Dopplers in major abdominal surgery | February 2001–May 2002 | Contacted – electronic version of poster provided |
| Kinsella[c] | Glasgow Royal Infirmary, UK | The effect of intraoperative fluid status guided by oesophageal Doppler monitoring on outcome of patients following urgent or emergency laparotomy | Not stated | Contacted – project abandoned at early stage; no information available |
| Merrick[d] | North Manchester General Hospital, UK | Clinical trial to assess whether transoesophageal Doppler monitoring can optimise intraoperative intravascular volume replacement and improve outcome in the surgical management of head and neck cancer patients | February–December 2002 | Contacted – project abandoned after unsuccessful pilot; no information available |
| Patey[e] | Aberdeen Royal Infirmary, UK | Perioperative fluid resuscitation guided by Doppler ultrasound stroke volume measurement in patients with hip fractures | February 1997–February 1998 | Contacted – study results not obtainable within timescale |
| Smith (Kong)[f] | Royal Sussex County Hospital, UK | Does haemodynamic optimisation, as guided by ODM, produce a greater reduction in complications and length of stay, if used intraoperatively, postoperatively, or both? | October 2006–October 2007 | Contacted – no response received |

a ClinicalTrials.gov NCT00444262.
b National Research Register N0186092455.
c Currrent Controlled Trial ISRCTN 11799696.
d National Research Register N0155107830.
e National Research Register N0411167547.
f National Research Register N0051189167.

# Health Technology Assessment reports published to date

**Volume 1, 1997**

**No. 1**
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

**No. 2**
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

**No. 3**
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

**No. 4**
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

**No. 5**
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al*.

**No. 6**
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

**No. 7**
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al*.

**No. 8**
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

**No. 9**
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

**No. 10**
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

**No. 11**
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al*.

**No. 12**
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

**No. 13**
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

**No. 14**
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

**Volume 2, 1998**

**No. 1**
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

**No. 2**
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

**No. 3**
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al*.

**No. 4**
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

**No. 5**
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al*.

**No. 6**
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

**No. 7**
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

**No. 8**
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

**No. 9**
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

**No. 10**
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

**No. 11**
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

**No. 12**
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

**No. 13**
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

**No. 14**
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

**No. 15**
Ethical issues in the design and conduct of randomised controlled trials.
A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

**No. 16**
Qualitative research methods in health technology assessment: a review of the literature.
By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

**No. 17**
The costs and benefits of paramedic skills in pre-hospital trauma care.
By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

**No. 18**
Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.
By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al*.

**No. 19**
Systematic reviews of trials and other studies.
By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

**No. 20**
Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.
A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al*.

### Volume 3, 1999

**No. 1**
Informed decision making: an annotated bibliography and systematic review.
By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al*.

**No. 2**
Handling uncertainty when performing economic evaluation of healthcare interventions.
A review by Briggs AH, Gray AM.

**No. 3**
The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

**No. 4**
A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.
By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al*.

**No. 5**
Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.
By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

**No. 6**
Assessing the costs of healthcare technologies in clinical trials.
A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

**No. 7**
Cooperatives and their primary care emergency centres: organisation and impact.
By Hallam L, Henthorne K.

**No. 8**
Screening for cystic fibrosis.
A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

**No. 9**
A review of the use of health status measures in economic evaluation.
By Brazier J, Deverill M, Green C, Harper R, Booth A.

**No. 10**
Methods for the analysis of quality-of-life and survival data in health technology assessment.
A review by Billingham LJ, Abrams KR, Jones DR.

**No. 11**
Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.
By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

**No. 12**
Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.
A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al*.

**No. 13**
'Early warning systems' for identifying new healthcare technologies.
By Robert G, Stevens A, Gabbay J.

**No. 14**
A systematic review of the role of human papillomavirus testing within a cervical screening programme.
By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al*.

**No. 15**
Near patient testing in diabetes clinics: appraising the costs and outcomes.
By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

**No. 16**
Positron emission tomography: establishing priorities for health technology assessment.
A review by Robert G, Milne R.

**No. 17 (Pt 1)**
The debridement of chronic wounds: a systematic review.
By Bradley M, Cullum N, Sheldon T.

**No. 17 (Pt 2)**
Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.
By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

**No. 18**
A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.
By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al*.

**No. 19**
What role for statins? A review and economic model.
By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al*.

**No. 20**
Factors that limit the quality, number and progress of randomised controlled trials.
A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al*.

**No. 21**
Antimicrobial prophylaxis in total hip replacement: a systematic review.
By Glenny AM, Song F.

**No. 22**
Health promoting schools and health promotion in schools: two systematic reviews.
By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

**No. 23**
Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.
A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

**Volume 4, 2000**

**No. 1**
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.
A review by Cairns JA, van der Pol MM.

**No. 2**
Geriatric rehabilitation following fractures in older people: a systematic review.
By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al*.

**No. 3**
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.
By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

**No. 4**
Community provision of hearing aids and related audiology services.
A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

**No. 5**
False-negative results in screening programmes: systematic review of impact and implications.
By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

**No. 6**
Costs and benefits of community postnatal support workers: a randomised controlled trial.
By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

**No. 7**
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.
By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al*.

**No. 8**
An introduction to statistical methods for health technology assessment.
A review by White SJ, Ashby D, Brown PJ.

**No. 9**
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.
By Clegg A, Bryant J, Milne R.

**No. 10**
Publication and related biases.
A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

**No. 11**
Cost and outcome implications of the organisation of vascular services.
By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

**No. 12**
Monitoring blood glucose control in diabetes mellitus: a systematic review.
By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

**No. 13**
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.
By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al*.

**No. 14**
The determinants of screening uptake and interventions for increasing uptake: a systematic review.
By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

**No. 15**
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.
A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

**No. 16**
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.
By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al*.

**No. 17**
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.
By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

**No. 18**
Liquid-based cytology in cervical screening: a rapid and systematic review.
By Payne N, Chilcott J, McGoogan E.

**No. 19**
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.
By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al*.

**No. 20**
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?
By Kerry S, Hilton S, Patel S, Dundas D, Rink E, Lord J.

**No. 21**
Systematic reviews of wound care management: (3) antimicrobial agents for chronic wounds; (4) diabetic foot ulceration.
By O'Meara S, Cullum N, Majid M, Sheldon T.

**No. 22**
Using routine data to complement and enhance the results of randomised controlled trials.
By Lewsey JD, Leyland AH, Murray GD, Boddy FA.

**No. 23**
Coronary artery stents in the treatment of ischaemic heart disease: a rapid and systematic review.
By Meads C, Cummins C, Jolly K, Stevens A, Burls A, Hyde C.

**No. 24**
Outcome measures for adult critical care: a systematic review.
By Hayes JA, Black NA, Jenkinson C, Young JD, Rowan KM, Daly K, *et al*.

**No. 25**
A systematic review to evaluate the effectiveness of interventions to promote the initiation of breastfeeding.
By Fairbank L, O'Meara S, Renfrew MJ, Woolridge M, Sowden AJ, Lister-Sharp D.

**No. 26**
Implantable cardioverter defibrillators: arrhythmias. A rapid and systematic review.
By Parkes J, Bryant J, Milne R.

**No. 27**
Treatments for fatigue in multiple sclerosis: a rapid and systematic review.
By Brañas P, Jordan R, Fry-Smith A, Burls A, Hyde C.

**No. 28**
Early asthma prophylaxis, natural history, skeletal development and economy (EASE): a pilot randomised controlled trial.
By Baxter-Jones ADG, Helms PJ, Russell G, Grant A, Ross S, Cairns JA, *et al*.

**No. 29**
Screening for hypercholesterolaemia versus case finding for familial hypercholesterolaemia: a systematic review and cost-effectiveness analysis.
By Marks D, Wonderling D, Thorogood M, Lambert H, Humphries SE, Neil HAW.

**No. 30**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists in the medical management of unstable angina.
By McDonagh MS, Bachmann LM, Golder S, Kleijnen J, ter Riet G.

**No. 31**
A randomised controlled trial of prehospital intravenous fluid replacement therapy in serious trauma.
By Turner J, Nicholl J, Webber L, Cox H, Dixon S, Yates D.

**No. 32**
Intrathecal pumps for giving opioids in chronic pain: a systematic review.
By Williams JE, Louw G, Towlerton G.

**No. 33**
Combination therapy (interferon alfa and ribavirin) in the treatment of chronic hepatitis C: a rapid and systematic review.
By Shepherd J, Waugh N, Hewitson P.

**No. 34**
A systematic review of comparisons of effect sizes derived from randomised and non-randomised studies.
By MacLehose RR, Reeves BC, Harvey IM, Sheldon TA, Russell IT, Black AMS.

**No. 35**
Intravascular ultrasound-guided interventions in coronary artery disease: a systematic literature review, with decision-analytic modelling, of outcomes and cost-effectiveness.
By Berry E, Kelly S, Hutton J, Lindsay HSJ, Blaxill JM, Evans JA, *et al*.

**No. 36**
A randomised controlled trial to evaluate the effectiveness and cost-effectiveness of counselling patients with chronic depression.
By Simpson S, Corney R, Fitzgerald P, Beecham J.

**No. 37**
Systematic review of treatments for atopic eczema.
By Hoare C, Li Wan Po A, Williams H.

**No. 38**
Bayesian methods in health technology assessment: a review.
By Spiegelhalter DJ, Myles JP, Jones DR, Abrams KR.

**No. 39**
The management of dyspepsia: a systematic review.
By Delaney B, Moayyedi P, Deeks J, Innes M, Soo S, Barton P, *et al*.

**No. 40**
A systematic review of treatments for severe psoriasis.
By Griffiths CEM, Clark CM, Chalmers RJG, Li Wan Po A, Williams HC.

## Volume 5, 2001

**No. 1**
Clinical and cost-effectiveness of donepezil, rivastigmine and galantamine for Alzheimer's disease: a rapid and systematic review.
By Clegg A, Bryant J, Nicholson T, McIntyre L, De Broe S, Gerard K, *et al*.

**No. 2**
The clinical effectiveness and cost-effectiveness of riluzole for motor neurone disease: a rapid and systematic review.
By Stewart A, Sandercock J, Bryan S, Hyde C, Barton PM, Fry-Smith A, *et al*.

**No. 3**
Equity and the economic evaluation of healthcare.
By Sassi F, Archard L, Le Grand J.

**No. 4**
Quality-of-life measures in chronic diseases of childhood.
By Eiser C, Morse R.

**No. 5**
Eliciting public preferences for healthcare: a systematic review of techniques.
By Ryan M, Scott DA, Reeves C, Bate A, van Teijlingen ER, Russell EM, *et al*.

**No. 6**
General health status measures for people with cognitive impairment: learning disability and acquired brain injury.
By Riemsma RP, Forbes CA, Glanville JM, Eastwood AJ, Kleijnen J.

**No. 7**
An assessment of screening strategies for fragile X syndrome in the UK.
By Pembrey ME, Barnicoat AJ, Carmichael B, Bobrow M, Turner G.

**No. 8**
Issues in methodological research: perspectives from researchers and commissioners.
By Lilford RJ, Richardson A, Stevens A, Fitzpatrick R, Edwards S, Rock F, *et al*.

**No. 9**
Systematic reviews of wound care management: (5) beds; (6) compression; (7) laser therapy, therapeutic ultrasound, electrotherapy and electromagnetic therapy.
By Cullum N, Nelson EA, Flemming K, Sheldon T.

**No. 10**
Effects of educational and psychosocial interventions for adolescents with diabetes mellitus: a systematic review.
By Hampson SE, Skinner TC, Hart J, Storey L, Gage H, Foxcroft D, *et al*.

**No. 11**
Effectiveness of autologous chondrocyte transplantation for hyaline cartilage defects in knees: a rapid and systematic review.
By Jobanputra P, Parry D, Fry-Smith A, Burls A.

**No. 12**
Statistical assessment of the learning curves of health technologies.
By Ramsay CR, Grant AM, Wallace SA, Garthwaite PH, Monk AF, Russell IT.

**No. 13**
The effectiveness and cost-effectiveness of temozolomide for the treatment of recurrent malignant glioma: a rapid and systematic review.
By Dinnes J, Cave C, Huang S, Major K, Milne R.

**No. 14**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of debriding agents in treating surgical wounds healing by secondary intention.
By Lewis R, Whiting P, ter Riet G, O'Meara S, Glanville J.

**No. 15**
Home treatment for mental health problems: a systematic review.
By Burns T, Knapp M, Catty J, Healey A, Henderson J, Watt H, *et al*.

**No. 16**
How to develop cost-conscious guidelines.
By Eccles M, Mason J.

**No. 17**
The role of specialist nurses in multiple sclerosis: a rapid and systematic review.
By De Broe S, Christopher F, Waugh N.

**No. 18**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of orlistat in the management of obesity.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

**No. 19**
The clinical effectiveness and cost-effectiveness of pioglitazone for type 2 diabetes mellitus: a rapid and systematic review.
By Chilcott J, Wight J, Lloyd Jones M, Tappenden P.

**No. 20**
Extended scope of nursing practice: a multicentre randomised controlled trial of appropriately trained nurses and preregistration house officers in preoperative assessment in elective general surgery.
By Kinley H, Czoski-Murray C, George S, McCabe C, Primrose J, Reilly C, *et al*.

**No. 21**
Systematic reviews of the effectiveness of day care for people with severe mental disorders: (1) Acute day hospital versus admission; (2) Vocational rehabilitation; (3) Day hospital versus outpatient care.
By Marshall M, Crowther R, Almaraz- Serrano A, Creed F, Sledge W, Kluiter H, *et al*.

**No. 22**
The measurement and monitoring of surgical adverse events.
By Bruce J, Russell EM, Mollison J, Krukowski ZH.

**No. 23**
Action research: a systematic review and guidance for assessment.
By Waterman H, Tillen D, Dickson R, de Koning K.

**No. 24**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of gemcitabine for the treatment of pancreatic cancer.
By Ward S, Morris E, Bansback N, Calvert N, Crellin A, Forman D, *et al*.

**No. 25**
A rapid and systematic review of the evidence for the clinical effectiveness and cost-effectiveness of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer.
By Lloyd Jones M, Hummel S, Bansback N, Orr B, Seymour M.

**No. 26**
Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature.
By Brocklebank D, Ram F, Wright J, Barry P, Cates C, Davies L, *et al*.

**No. 27**
The cost-effectiveness of magnetic resonance imaging for investigation of the knee joint.
By Bryan S, Weatherburn G, Bungay H, Hatrick C, Salas C, Parry D, *et al*.

**No. 28**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of topotecan for ovarian cancer.
By Forbes C, Shirran L, Bagnall A-M, Duffy S, ter Riet G.

**No. 29**
Superseded by a report published in a later volume.

**No. 30**
The role of radiography in primary care patients with low back pain of at least 6 weeks duration: a randomised (unblinded) controlled trial.
By Kendrick D, Fielding K, Bentley E, Miller P, Kerslake R, Pringle M.

**No. 31**
Design and use of questionnaires: a review of best practice applicable to surveys of health service staff and patients.
By McColl E, Jacoby A, Thomas L, Soutter J, Bamford C, Steen N, *et al*.

**No. 32**
A rapid and systematic review of the clinical effectiveness and cost-effectiveness of paclitaxel, docetaxel, gemcitabine and vinorelbine in non-small-cell lung cancer.
By Clegg A, Scott DA, Sidhu M, Hewitson P, Waugh N.

**No. 33**
Subgroup analyses in randomised controlled trials: quantifying the risks of false-positives and false-negatives.
By Brookes ST, Whitley E, Peters TJ, Mulheran PA, Egger M, Davey Smith G.

**No. 34**
Depot antipsychotic medication in the treatment of patients with schizophrenia: (1) Meta-review; (2) Patient and nurse attitudes.
By David AS, Adams C.

**No. 35**
A systematic review of controlled trials of the effectiveness and cost-effectiveness of brief psychological treatments for depression.
By Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, *et al*.

**No. 36**
Cost analysis of child health surveillance.
By Sanderson D, Wright D, Acton C, Duree D.

## Volume 6, 2002

**No. 1**
A study of the methods used to select review criteria for clinical audit.
By Hearnshaw H, Harker R, Cheater F, Baker R, Grimshaw G.

**No. 2**
Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.
By Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, *et al*.

**No. 3**
Rituximab as third-line treatment for refractory or recurrent Stage III or IV follicular non-Hodgkin's lymphoma: a systematic review and economic evaluation.
By Wake B, Hyde C, Bryan S, Barton P, Song F, Fry-Smith A, *et al*.

**No. 4**
A systematic review of discharge arrangements for older people.
By Parker SG, Peet SM, McPherson A, Cannaby AM, Baker R, Wilson A, *et al*.

**No. 5**
The clinical effectiveness and cost-effectiveness of inhaler devices used in the routine management of chronic asthma in older children: a systematic review and economic evaluation.
By Peters J, Stevenson M, Beverley C, Lim J, Smith S.

**No. 6**
The clinical effectiveness and cost-effectiveness of sibutramine in the management of obesity: a technology assessment.
By O'Meara S, Riemsma R, Shirran L, Mather L, ter Riet G.

**No. 7**
The cost-effectiveness of magnetic resonance angiography for carotid artery stenosis and peripheral vascular disease: a systematic review.
By Berry E, Kelly S, Westwood ME, Davies LM, Gough MJ, Bamford JM, *et al*.

**No. 8**
Promoting physical activity in South Asian Muslim women through 'exercise on prescription'.
By Carroll B, Ali N, Azam N.

**No. 9**
Zanamivir for the treatment of influenza in adults: a systematic review and economic evaluation.
By Burls A, Clark W, Stewart T, Preston C, Bryan S, Jefferson T, *et al*.

**No. 10**
A review of the natural history and epidemiology of multiple sclerosis: implications for resource allocation and health economic models.
By Richards RG, Sampson FC, Beard SM, Tappenden P.

**No. 11**
Screening for gestational diabetes: a systematic review and economic evaluation.
By Scott DA, Loveman E, McIntyre L, Waugh N.

**No. 12**
The clinical effectiveness and cost-effectiveness of surgery for people with morbid obesity: a systematic review and economic evaluation.
By Clegg AJ, Colquitt J, Sidhu MK, Royle P, Loveman E, Walker A.

**No. 13**
The clinical effectiveness of trastuzumab for breast cancer: a systematic review.
By Lewis R, Bagnall A-M, Forbes C, Shirran E, Duffy S, Kleijnen J, *et al*.

**No. 14**
The clinical effectiveness and cost-effectiveness of vinorelbine for breast cancer: a systematic review and economic evaluation.
By Lewis R, Bagnall A-M, King S, Woolacott N, Forbes C, Shirran L, *et al*.

**No. 15**
A systematic review of the effectiveness and cost-effectiveness of metal-on-metal hip resurfacing arthroplasty for treatment of hip disease.
By Vale L, Wyness L, McCormack K, McKenzie L, Brazzelli M, Stearns SC.

**No. 16**
The clinical effectiveness and cost-effectiveness of bupropion and nicotine replacement therapy for smoking cessation: a systematic review and economic evaluation.
By Woolacott NF, Jones L, Forbes CA, Mather LC, Sowden AJ, Song FJ, *et al*.

**No. 17**
A systematic review of effectiveness and economic evaluation of new drug treatments for juvenile idiopathic arthritis: etanercept.
By Cummins C, Connock M, Fry-Smith A, Burls A.

**No. 18**
Clinical effectiveness and cost-effectiveness of growth hormone in children: a systematic review and economic evaluation.
By Bryant J, Cave C, Mihaylova B, Chase D, McIntyre L, Gerard K, *et al*.

**No. 19**
Clinical effectiveness and cost-effectiveness of growth hormone in adults in relation to impact on quality of life: a systematic review and economic evaluation.
By Bryant J, Loveman E, Chase D, Mihaylova B, Cave C, Gerard K, *et al*.

**No. 20**
Clinical medication review by a pharmacist of patients on repeat prescriptions in general practice: a randomised controlled trial.
By Zermansky AG, Petty DR, Raynor DK, Lowe CJ, Freementle N, Vail A.

**No. 21**
The effectiveness of infliximab and etanercept for the treatment of rheumatoid arthritis: a systematic review and economic evaluation.
By Jobanputra P, Barton P, Bryan S, Burls A.

**No. 22**
A systematic review and economic evaluation of computerised cognitive behaviour therapy for depression and anxiety.
By Kaltenthaler E, Shackley P, Stevens K, Beverley C, Parry G, Chilcott J.

**No. 23**
A systematic review and economic evaluation of pegylated liposomal doxorubicin hydrochloride for ovarian cancer.
By Forbes C, Wilby J, Richardson G, Sculpher M, Mather L, Reimsma R.

**No. 24**
A systematic review of the effectiveness of interventions based on a stages-of-change approach to promote individual behaviour change.
By Riemsma RP, Pattenden J, Bridle C, Sowden AJ, Mather L, Watt IS, *et al*.

**No. 25**
A systematic review update of the clinical effectiveness and cost-effectiveness of glycoprotein IIb/IIIa antagonists.
By Robinson M, Ginnelly L, Sculpher M, Jones L, Riemsma R, Palmer S, *et al*.

**No. 26**
A systematic review of the effectiveness, cost-effectiveness and barriers to implementation of thrombolytic and neuroprotective therapy for acute ischaemic stroke in the NHS.
By Sandercock P, Berge E, Dennis M, Forbes J, Hand P, Kwan J, *et al*.

**No. 27**
A randomised controlled crossover trial of nurse practitioner versus doctor-led outpatient care in a bronchiectasis clinic.
By Caine N, Sharples LD, Hollingworth W, French J, Keogan M, Exley A, *et al*.

**No. 28**
Clinical effectiveness and cost – consequences of selective serotonin reuptake inhibitors in the treatment of sex offenders.
By Adi Y, Ashcroft D, Browne K, Beech A, Fry-Smith A, Hyde C.

**No. 29**
Treatment of established osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Brazier JE, Stevenson M, Calvert NW, Lloyd Jones M.

**No. 30**
Which anaesthetic agents are cost-effective in day surgery? Literature review, national survey of practice and randomised controlled trial.
By Elliott RA Payne K, Moore JK, Davies LM, Harper NJN, St Leger AS, *et al*.

**No. 31**
Screening for hepatitis C among injecting drug users and in genitourinary medicine clinics: systematic reviews of effectiveness, modelling study and national survey of current practice.
By Stein K, Dalziel K, Walker A, McIntyre L, Jenkins B, Horne J, *et al*.

**No. 32**
The measurement of satisfaction with healthcare: implications for practice from a systematic review of the literature.
By Crow R, Gage H, Hampson S, Hart J, Kimber A, Storey L, *et al*.

**No. 33**
The effectiveness and cost-effectiveness of imatinib in chronic myeloid leukaemia: a systematic review.
By Garside R, Round A, Dalziel K, Stein K, Royle R.

**No. 34**
A comparative study of hypertonic saline, daily and alternate-day rhDNase in children with cystic fibrosis.
By Suri R, Wallis C, Bush A, Thompson S, Normand C, Flather M, *et al*.

**No. 35**
A systematic review of the costs and effectiveness of different models of paediatric home care.
By Parker G, Bhakta P, Lovett CA, Paisley S, Olsen R, Turner D, *et al*.

## Volume 7, 2003

**No. 1**
How important are comprehensive literature searches and the assessment of trial quality in systematic reviews? Empirical study.
By Egger M, Jüni P, Bartlett C, Holenstein F, Sterne J.

**No. 2**
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of home versus hospital or satellite unit haemodialysis for people with end-stage renal failure.
By Mowatt G, Vale L, Perez J, Wyness L, Fraser C, MacLeod A, *et al*.

**No. 3**
Systematic review and economic evaluation of the effectiveness of infliximab for the treatment of Crohn's disease.
By Clark W, Raftery J, Barton P, Song F, Fry-Smith A, Burls A.

**No. 4**
A review of the clinical effectiveness and cost-effectiveness of routine anti-D prophylaxis for pregnant women who are rhesus negative.
By Chilcott J, Lloyd Jones M, Wight J, Forman K, Wray J, Beverley C, *et al*.

**No. 5**
Systematic review and evaluation of the use of tumour markers in paediatric oncology: Ewing's sarcoma and neuroblastoma.
By Riley RD, Burchill SA, Abrams KR, Heney D, Lambert PC, Jones DR, *et al*.

**No. 6**
The cost-effectiveness of screening for *Helicobacter pylori* to reduce mortality and morbidity from gastric cancer and peptic ulcer disease: a discrete-event simulation model.
By Roderick P, Davies R, Raftery J, Crabbe D, Pearce R, Bhandari P, *et al*.

**No. 7**
The clinical effectiveness and cost-effectiveness of routine dental checks: a systematic review and economic evaluation.
By Davenport C, Elley K, Salas C, Taylor-Weetman CL, Fry-Smith A, Bryan S, *et al*.

**No. 8**
A multicentre randomised controlled trial assessing the costs and benefits of using structured information and analysis of women's preferences in the management of menorrhagia.
By Kennedy ADM, Sculpher MJ, Coulter A, Dwyer N, Rees M, Horsley S, *et al*.

**No. 9**
Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation.
By Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C.

**No. 10**
Evaluation of molecular tests for prenatal diagnosis of chromosome abnormalities.
By Grimshaw GM, Szczepura A, Hultén M, MacDonald F, Nevin NC, Sutton F, *et al*.

**No. 11**
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).
By Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

**No. 12**
The effectiveness and cost-effectiveness of ultrasound locating devices for central venous access: a systematic review and economic evaluation.
By Calvert N, Hind D, McWilliams RG, Thomas SM, Beverley C, Davidson A.

**No. 13**
A systematic review of atypical antipsychotics in schizophrenia.
By Bagnall A-M, Jones L, Lewis R, Ginnelly L, Glanville J, Torgerson D, *et al.*

**No. 14**
Prostate Testing for Cancer and Treatment (ProtecT) feasibility study.
By Donovan J, Hamdy F, Neal D, Peters T, Oliver S, Brindle L, *et al*.

**No. 15**
Early thrombolysis for the treatment of acute myocardial infarction: a systematic review and economic evaluation.
By Boland A, Dundar Y, Bagust A, Haycox A, Hill R, Mujica Mota R, *et al*.

**No. 16**
Screening for fragile X syndrome: a literature review and modelling.
By Song FJ, Barton P, Sleightholme V, Yao GL, Fry-Smith A.

**No. 17**
Systematic review of endoscopic sinus surgery for nasal polyps.
By Dalziel K, Stein K, Round A, Garside R, Royle P.

**No. 18**
Towards efficient guidelines: how to monitor guideline use in primary care.
By Hutchinson A, McIntosh A, Cox S, Gilbert C.

**No. 19**
Effectiveness and cost-effectiveness of acute hospital-based spinal cord injuries services: systematic review.
By Bagnall A-M, Jones L, Richardson G, Duffy S, Riemsma R.

**No. 20**
Prioritisation of health technology assessment. The PATHS model: methods and case studies.
By Townsend J, Buxton M, Harper G.

**No. 21**
Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence.
By Cody J, Wyness L, Wallace S, Glazener C, Kilonzo M, Stearns S, *et al*.

**No. 22**
The clinical and cost-effectiveness of patient education models for diabetes: a systematic review and economic evaluation.
By Loveman E, Cave C, Green C, Royle P, Dunn N, Waugh N.

**No. 23**
The role of modelling in prioritising and planning clinical trials.
By Chilcott J, Brennan A, Booth A, Karnon J, Tappenden P.

**No. 24**
Cost–benefit evaluation of routine influenza immunisation in people 65–74 years of age.
By Allsup S, Gosney M, Haycox A, Regan M.

**No. 25**
The clinical and cost-effectiveness of pulsatile machine perfusion versus cold storage of kidneys for transplantation retrieved from heart-beating and non-heart-beating donors.
By Wight J, Chilcott J, Holmes M, Brewer N.

**No. 26**
Can randomised trials rely on existing electronic data? A feasibility study to explore the value of routine data in health technology assessment.
By Williams JG, Cheung WY, Cohen DR, Hutchings HA, Longo MF, Russell IT.

**No. 27**
Evaluating non-randomised intervention studies.
By Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al*.

**No. 28**
A randomised controlled trial to assess the impact of a package comprising a patient-orientated, evidence-based self-help guidebook and patient-centred consultations on disease management and satisfaction in inflammatory bowel disease.
By Kennedy A, Nelson E, Reeves D, Richardson G, Roberts C, Robinson A, *et al*.

**No. 29**
The effectiveness of diagnostic tests for the assessment of shoulder pain due to soft tissue disorders: a systematic review.
By Dinnes J, Loveman E, McIntyre L, Waugh N.

**No. 30**
The value of digital imaging in diabetic retinopathy.
By Sharp PF, Olson J, Strachan F, Hipwell J, Ludbrook A, O'Donnell M, *et al*.

**No. 31**
Lowering blood pressure to prevent myocardial infarction and stroke: a new preventive strategy.
By Law M, Wald N, Morris J.

**No. 32**
Clinical and cost-effectiveness of capecitabine and tegafur with uracil for the treatment of metastatic colorectal cancer: systematic review and economic evaluation.
By Ward S, Kaltenthaler E, Cowan J, Brewer N.

**No. 33**
Clinical and cost-effectiveness of new and emerging technologies for early localised prostate cancer: a systematic review.
By Hummel S, Paisley S, Morgan A, Currie E, Brewer N.

**No. 34**
Literature searching for clinical and cost-effectiveness studies used in health technology assessment reports carried out for the National Institute for Clinical Excellence appraisal system.
By Royle P, Waugh N.

**No. 35**
Systematic review and economic decision modelling for the prevention and treatment of influenza A and B.
By Turner D, Wailoo A, Nicholson K, Cooper N, Sutton A, Abrams K.

**No. 36**
A randomised controlled trial to evaluate the clinical and cost-effectiveness of Hickman line insertions in adult cancer patients by nurses.
By Boland A, Haycox A, Bagust A, Fitzsimmons L.

**No. 37**
Redesigning postnatal care: a randomised controlled trial of protocol-based midwifery-led care focused on individual women's physical and psychological health needs.
By MacArthur C, Winter HR, Bick DE, Lilford RJ, Lancashire RJ, Knowles H, *et al*.

**No. 38**
Estimating implied rates of discount in healthcare decision-making.
By West RR, McNabb R, Thompson AGH, Sheldon TA, Grimley Evans J.

**No. 39**
Systematic review of isolation policies in the hospital management of methicillin-resistant *Staphylococcus aureus*: a review of the literature with epidemiological and economic modelling.
By Cooper BS, Stone SP, Kibbler CC, Cookson BD, Roberts JA, Medley GF, *et al*.

**No. 40**
Treatments for spasticity and pain in multiple sclerosis: a systematic review.
By Beard S, Hunn A, Wight J.

**No. 41**
The inclusion of reports of randomised trials published in languages other than English in systematic reviews.
By Moher D, Pham B, Lawson ML, Klassen TP.

**No. 42**
The impact of screening on future health-promoting behaviours and health beliefs: a systematic review.
By Bankhead CR, Brett J, Bukach C, Webster P, Stewart-Brown S, Munafo M, *et al*.

### Volume 8, 2004

**No. 1**
What is the best imaging strategy for acute stroke?
By Wardlaw JM, Keir SL, Seymour J, Lewis S, Sandercock PAG, Dennis MS, *et al*.

**No. 2**
Systematic review and modelling of the investigation of acute and chronic chest pain presenting in primary care.
By Mant J, McManus RJ, Oakes RAL, Delaney BC, Barton PM, Deeks JJ, *et al*.

**No. 3**
The effectiveness and cost-effectiveness of microwave and thermal balloon endometrial ablation for heavy menstrual bleeding: a systematic review and economic modelling.
By Garside R, Stein K, Wyatt K, Round A, Price A.

**No. 4**
A systematic review of the role of bisphosphonates in metastatic disease.
By Ross JR, Saunders Y, Edmonds PM, Patel S, Wonderling D, Normand C, *et al*.

**No. 5**
Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer.
By Jones L, Hawkins N, Westwood M, Wright K, Richardson G, Riemsma R.

**No. 6**
Effectiveness and efficiency of guideline dissemination and implementation strategies.
By Grimshaw JM, Thomas RE, MacLennan G, Fraser C, Ramsay CR, Vale L, *et al*.

**No. 7**
Clinical effectiveness and costs of the Sugarbaker procedure for the treatment of pseudomyxoma peritonei.
By Bryant J, Clegg AJ, Sidhu MK, Brodin H, Royle P, Davidson P.

**No. 8**
Psychological treatment for insomnia in the regulation of long-term hypnotic drug use.
By Morgan K, Dixon S, Mathers N, Thompson J, Tomeny M.

**No. 9**
Improving the evaluation of therapeutic interventions in multiple sclerosis: development of a patient-based measure of outcome.
By Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ.

**No. 10**
A systematic review and economic evaluation of magnetic resonance cholangiopancreatography compared with diagnostic endoscopic retrograde cholangiopancreatography.
By Kaltenthaler E, Bravo Vergel Y, Chilcott J, Thomas S, Blakeborough T, Walters SJ, *et al*.

**No. 11**
The use of modelling to evaluate new drugs for patients with a chronic condition: the case of antibodies against tumour necrosis factor in rheumatoid arthritis.
By Barton P, Jobanputra P, Wilson J, Bryan S, Burls A.

**No. 12**
Clinical effectiveness and cost-effectiveness of neonatal screening for inborn errors of metabolism using tandem mass spectrometry: a systematic review.
By Pandor A, Eastham J, Beverley C, Chilcott J, Paisley S.

**No. 13**
Clinical effectiveness and cost-effectiveness of pioglitazone and rosiglitazone in the treatment of type 2 diabetes: a systematic review and economic evaluation.
By Czoski-Murray C, Warren E, Chilcott J, Beverley C, Psyllaki MA, Cowan J.

**No. 14**
Routine examination of the newborn: the EMREN study. Evaluation of an extension of the midwife role including a randomised controlled trial of appropriately trained midwives and paediatric senior house officers.
By Townsend J, Wolke D, Hayes J, Davé S, Rogers C, Bloomfield L, *et al*.

**No. 15**
Involving consumers in research and development agenda setting for the NHS: developing an evidence-based approach.
By Oliver S, Clarke-Jones L, Rees R, Milne R, Buchanan P, Gabbay J, *et al*.

**No. 16**
A multi-centre randomised controlled trial of minimally invasive direct coronary bypass grafting versus percutaneous transluminal coronary angioplasty with stenting for proximal stenosis of the left anterior descending coronary artery.
By Reeves BC, Angelini GD, Bryan AJ, Taylor FC, Cripps T, Spyt TJ, *et al*.

**No. 17**
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.
By Gilbert FJ, Grant AM, Gillan MGC, Vale L, Scott NW, Campbell MK, *et al*.

**No. 18**
The clinical and cost-effectiveness of anakinra for the treatment of rheumatoid arthritis in adults: a systematic review and economic analysis.
By Clark W, Jobanputra P, Barton P, Burls A.

**No. 19**
A rapid and systematic review and economic evaluation of the clinical and cost-effectiveness of newer drugs for treatment of mania associated with bipolar affective disorder.
By Bridle C, Palmer S, Bagnall A-M, Darba J, Duffy S, Sculpher M, *et al*.

**No. 20**
Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis.
By Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N.

**No. 21**
Systematic review of the long-term effects and economic consequences of treatments for obesity and implications for health improvement.
By Avenell A, Broom J, Brown TJ, Poobalan A, Aucott L, Stearns SC, *et al*.

**No. 22**
Autoantibody testing in children with newly diagnosed type 1 diabetes mellitus.
By Dretzke J, Cummins C, Sandercock J, Fry-Smith A, Barrett T, Burls A.

**No. 23**
Clinical effectiveness and cost-effectiveness of prehospital intravenous fluids in trauma patients.
By Dretzke J, Sandercock J, Bayliss S, Burls A.

**No. 24**
Newer hypnotic drugs for the short-term management of insomnia: a systematic review and economic evaluation.
By Dündar Y, Boland A, Strobl J, Dodd S, Haycox A, Bagust A, *et al*.

**No. 25**
Development and validation of methods for assessing the quality of diagnostic accuracy studies.
By Whiting P, Rutjes AWS, Dinnes J, Reitsma JB, Bossuyt PMM, Kleijnen J.

**No. 26**
EVALUATE hysterectomy trial: a multicentre randomised trial comparing abdominal, vaginal and laparoscopic methods of hysterectomy.
By Garry R, Fountain J, Brown J, Manca A, Mason S, Sculpher M, *et al*.

**No. 27**
Methods for expected value of information analysis in complex health economic models: developments on the health economics of interferon-β and glatiramer acetate for multiple sclerosis.
By Tappenden P, Chilcott JB, Eggington S, Oakley J, McCabe C.

**No. 28**
Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis.
By Dalziel K, Round A, Stein K, Garside R, Price A.

**No. 29**
VenUS I: a randomised controlled trial of two types of bandage for treating venous leg ulcers.
By Iglesias C, Nelson EA, Cullum NA, Torgerson DJ, on behalf of the VenUS Team.

**No. 30**
Systematic review of the effectiveness and cost-effectiveness, and economic evaluation, of myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction.
By Mowatt G, Vale L, Brazzelli M, Hernandez R, Murray A, Scott N, *et al*.

**No. 31**
A pilot study on the use of decision theory and value of information analysis as part of the NHS Health Technology Assessment programme.
By Claxton K, Ginnelly L, Sculpher M, Philips Z, Palmer S.

**No. 32**
The Social Support and Family Health Study: a randomised controlled trial and economic evaluation of two alternative forms of postnatal support for mothers living in disadvantaged inner-city areas.
By Wiggins M, Oakley A, Roberts I, Turner H, Rajan L, Austerberry H, *et al*.

**No. 33**
Psychosocial aspects of genetic screening of pregnant women and newborns: a systematic review.
By Green JM, Hewison J, Bekker HL, Bryant, Cuckle HS.

**No. 34**
Evaluation of abnormal uterine bleeding: comparison of three outpatient procedures within cohorts defined by age and menopausal status.
By Critchley HOD, Warner P, Lee AJ, Brechin S, Guise J, Graham B.

**No. 35**
Coronary artery stents: a rapid systematic review and economic evaluation.
By Hill R, Bagust A, Bakhai A, Dickson R, Dündar Y, Haycox A, *et al*.

**No. 36**
Review of guidelines for good practice in decision-analytic modelling in health technology assessment.
By Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*.

**No. 37**
Rituximab (MabThera®) for aggressive non-Hodgkin's lymphoma: systematic review and economic evaluation.
By Knight C, Hind D, Brewer N, Abbott V.

**No. 38**
Clinical effectiveness and cost-effectiveness of clopidogrel and modified-release dipyridamole in the secondary prevention of occlusive vascular events: a systematic review and economic evaluation.
By Jones L, Griffin S, Palmer S, Main C, Orton V, Sculpher M, *et al.*

**No. 39**
Pegylated interferon α-2a and -2b in combination with ribavirin in the treatment of chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Brodin H, Cave C, Waugh N, Price A, Gabbay J.

**No. 40**
Clopidogrel used in combination with aspirin compared with aspirin alone in the treatment of non-ST-segment-elevation acute coronary syndromes: a systematic review and economic evaluation.
By Main C, Palmer S, Griffin S, Jones L, Orton V, Sculpher M, *et al.*

**No. 41**
Provision, uptake and cost of cardiac rehabilitation programmes: improving services to under-represented groups.
By Beswick AD, Rees K, Griebsch I, Taylor FC, Burke M, West RR, *et al.*

**No. 42**
Involving South Asian patients in clinical trials.
By Hussain-Gambles M, Leese B, Atkin K, Brown J, Mason S, Tovey P.

**No. 43**
Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes.
By Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N.

**No. 44**
Identification and assessment of ongoing trials in health technology assessment reviews.
By Song FJ, Fry-Smith A, Davenport C, Bayliss S, Adi Y, Wilson JS, *et al*.

**No. 45**
Systematic review and economic evaluation of a long-acting insulin analogue, insulin glargine
By Warren E, Weatherley-Jones E, Chilcott J, Beverley C.

**No. 46**
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.
By McCarthy CJ, Mills PM, Pullen R, Richardson G, Hawkins N, Roberts CR, *et al*.

**No. 47**
Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation.
By Green C, Colquitt JL, Kirby J, Davidson P, Payne E.

**No. 48**
Acupuncture of chronic headache disorders in primary care: randomised controlled trial and economic analysis.
By Vickers AJ, Rees RW, Zollman CE, McCarney R, Smith CM, Ellis N, *et al*.

**No. 49**
Generalisability in economic evaluation studies in healthcare: a review and case studies.
By Sculpher MJ, Pang FS, Manca A, Drummond MF, Golder S, Urdahl H, *et al*.

**No. 50**
Virtual outreach: a randomised controlled trial and economic evaluation of joint teleconferenced medical consultations.
By Wallace P, Barber J, Clayton W, Currell R, Fleming K, Garner P, *et al*.

### Volume 9, 2005

**No. 1**
Randomised controlled multiple treatment comparison to provide a cost-effectiveness rationale for the selection of antimicrobial therapy in acne.
By Ozolins M, Eady EA, Avery A, Cunliffe WJ, O'Neill C, Simpson NB, *et al*.

**No. 2**
Do the findings of case series studies vary significantly according to methodological characteristics?
By Dalziel K, Round A, Stein K, Garside R, Castelnuovo E, Payne L.

**No. 3**
Improving the referral process for familial breast cancer genetic counselling: findings of three randomised controlled trials of two interventions.
By Wilson BJ, Torrance N, Mollison J, Wordsworth S, Gray JR, Haites NE, *et al*.

**No. 4**
Randomised evaluation of alternative electrosurgical modalities to treat bladder outflow obstruction in men with benign prostatic hyperplasia.
By Fowler C, McAllister W, Plail R, Karim O, Yang Q.

**No. 5**
A pragmatic randomised controlled trial of the cost-effectiveness of palliative therapies for patients with inoperable oesophageal cancer.
By Shenfine J, McNamee P, Steen N, Bond J, Griffin SM.

**No. 6**
Impact of computer-aided detection prompts on the sensitivity and specificity of screening mammography.
By Taylor P, Champness J, Given-Wilson R, Johnston K, Potts H.

**No. 7**
Issues in data monitoring and interim analysis of trials.
By Grant AM, Altman DG, Babiker AB, Campbell MK, Clemens FJ, Darbyshire JH, *et al*.

**No. 8**
Lay public's understanding of equipoise and randomisation in randomised controlled trials.
By Robinson EJ, Kerr CEP, Stevens AJ, Lilford RJ, Braunholtz DA, Edwards SJ, *et al*.

**No. 9**
Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies.
By Greenhalgh J, Knight C, Hind D, Beverley C, Walters S.

**No. 10**
Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology.
By Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, *et al*.

**No. 11**
Clinical effectiveness and cost-effectiveness of drotrecogin alfa (activated) (Xigris®) for the treatment of severe sepsis in adults: a systematic review and economic evaluation.
By Green C, Dinnes J, Takeda A, Shepherd J, Hartwell D, Cave C, *et al*.

**No. 12**
A methodological review of how heterogeneity has been examined in systematic reviews of diagnostic test accuracy.
By Dinnes J, Deeks J, Kirby J, Roderick P.

**No. 13**
Cervical screening programmes: can automation help? Evidence from systematic reviews, an economic analysis and a simulation modelling exercise applied to the UK.
By Willis BH, Barton P, Pearmain P, Bryan S, Hyde C.

**No. 14**
Laparoscopic surgery for inguinal hernia repair: systematic review of effectiveness and economic evaluation.
By McCormack K, Wake B, Perez J, Fraser C, Cook J, McIntosh E, *et al*.

**No. 15**
Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation.
By Wilby J, Kainth A, Hawkins N, Epstein D, McIntosh H, McDaid C, *et al*.

**No. 16**
A randomised controlled trial to compare the cost-effectiveness of tricyclic antidepressants, selective serotonin reuptake inhibitors and lofepramine.
By Peveler R, Kendrick T, Buxton M, Longworth L, Baldwin D, Moore M, *et al*.

**No. 17**
Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation.
By Hartwell D, Colquitt J, Loveman E, Clegg AJ, Brodin H, Waugh N, *et al*.

**No. 18**
A randomised controlled comparison of alternative strategies in stroke care.
By Kalra L, Evans A, Perez I, Knapp M, Swift C, Donaldson N.

**No. 19**
The investigation and analysis of critical incidents and adverse events in healthcare.
By Woloshynowych M, Rogers S, Taylor-Adams S, Vincent C.

**No. 20**
Potential use of routine databases in health technology assessment.
By Raftery J, Roderick P, Stevens A.

**No. 21**
Clinical and cost-effectiveness of newer immunosuppressive regimens in renal transplantation: a systematic review and modelling study.
By Woodroffe R, Yao GL, Meads C, Bayliss S, Ready A, Raftery J, *et al*.

**No. 22**
A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.
By Stevenson M, Lloyd Jones M, De Nigris E, Brewer N, Davis S, Oakley J.

**No. 23**
A systematic review to examine the impact of psycho-educational interventions on health outcomes and costs in adults and children with difficult asthma.
By Smith JR, Mugford M, Holland R, Candy B, Noble MJ, Harrison BDW, *et al*.

**No. 24**
An evaluation of the costs, effectiveness and quality of renal replacement therapy provision in renal satellite units in England and Wales.
By Roderick P, Nicholson T, Armitage A, Mehta R, Mullee M, Gerard K, *et al*.

**No. 25**
Imatinib for the treatment of patients with unresectable and/or metastatic gastrointestinal stromal tumours: systematic review and economic evaluation.
By Wilson J, Connock M, Song F, Yao G, Fry-Smith A, Raftery J, *et al*.

**No. 26**
Indirect comparisons of competing interventions.
By Glenny AM, Altman DG, Song F, Sakarovitch C, Deeks JJ, D'Amico R, *et al*.

**No. 27**
Cost-effectiveness of alternative strategies for the initial medical management of non-ST elevation acute coronary syndrome: systematic review and decision-analytical modelling.
By Robinson M, Palmer S, Sculpher M, Philips Z, Ginnelly L, Bowens A, *et al*.

**No. 28**
Outcomes of electrically stimulated gracilis neosphincter surgery.
By Tillin T, Chambers M, Feldman R.

**No. 29**
The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation.
By Garside R, Stein K, Castelnuovo E, Pitt M, Ashcroft D, Dimmock P, *et al*.

**No. 30**
Systematic review on urine albumin testing for early detection of diabetic complications.
By Newman DJ, Mattock MB, Dawnay ABS, Kerry S, McGuire A, Yaqoob M, *et al*.

**No. 31**
Randomised controlled trial of the cost-effectiveness of water-based therapy for lower limb osteoarthritis.
By Cochrane T, Davey RC, Matthes Edwards SM.

**No. 32**
Longer term clinical and economic benefits of offering acupuncture care to patients with chronic low back pain.
By Thomas KJ, MacPherson H, Ratcliffe J, Thorpe L, Brazier J, Campbell M, *et al*.

**No. 33**
Cost-effectiveness and safety of epidural steroids in the management of sciatica.
By Price C, Arden N, Coglan L, Rogers P.

**No. 34**
The British Rheumatoid Outcome Study Group (BROSG) randomised controlled trial to compare the effectiveness and cost-effectiveness of aggressive versus symptomatic therapy in established rheumatoid arthritis.
By Symmons D, Tricker K, Roberts C, Davies L, Dawes P, Scott DL.

**No. 35**
Conceptual framework and systematic review of the effects of participants' and professionals' preferences in randomised controlled trials.
By King M, Nazareth I, Lampe F, Bower P, Chandler M, Morou M, *et al*.

**No. 36**
The clinical and cost-effectiveness of implantable cardioverter defibrillators: a systematic review.
By Bryant J, Brodin H, Loveman E, Payne E, Clegg A.

**No. 37**
A trial of problem-solving by community mental health nurses for anxiety, depression and life difficulties among general practice patients. The CPN-GP study.
By Kendrick T, Simons L, Mynors-Wallis L, Gray A, Lathlean J, Pickering R, *et al*.

**No. 38**
The causes and effects of socio-demographic exclusions from clinical trials.
By Bartlett C, Doyal L, Ebrahim S, Davey P, Bachmann M, Egger M, *et al*.

**No. 39**
Is hydrotherapy cost-effective? A randomised controlled trial of combined hydrotherapy programmes compared with physiotherapy land techniques in children with juvenile idiopathic arthritis.
By Epps H, Ginnelly L, Utley M, Southwood T, Gallivan S, Sculpher M, *et al*.

**No. 40**
A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study.
By Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, *et al*.

**No. 41**
Displaced intracapsular hip fractures in fit, older people: a randomised comparison of reduction and fixation, bipolar hemiarthroplasty and total hip arthroplasty.
By Keating JF, Grant A, Masson M, Scott NW, Forbes JF.

**No. 42**
Long-term outcome of cognitive behaviour therapy clinical trials in central Scotland.
By Durham RC, Chambers JA, Power KG, Sharp DM, Macdonald RR, Major KA, *et al*.

**No. 43**
The effectiveness and cost-effectiveness of dual-chamber pacemakers compared with single-chamber pacemakers for bradycardia due to atrioventricular block or sick sinus syndrome: systematic review and economic evaluation.
By Castelnuovo E, Stein K, Pitt M, Garside R, Payne E.

**No. 44**
Newborn screening for congenital heart defects: a systematic review and cost-effectiveness analysis.
By Knowles R, Griebsch I, Dezateux C, Brown J, Bull C, Wren C.

**No. 45**
The clinical and cost-effectiveness of left ventricular assist devices for end-stage heart failure: a systematic review and economic evaluation.
By Clegg AJ, Scott DA, Loveman E, Colquitt J, Hutchinson J, Royle P, *et al*.

**No. 46**
The effectiveness of the Heidelberg Retina Tomograph and laser diagnostic glaucoma scanning system (GDx) in detecting and monitoring glaucoma.
By Kwartz AJ, Henson DB, Harper RA, Spencer AF, McLeod D.

**No. 47**
Clinical and cost-effectiveness of autologous chondrocyte implantation for cartilage defects in knee joints: systematic review and economic evaluation.
By Clar C, Cummins E, McIntyre L, Thomas S, Lamb J, Bain L, *et al*.

**No. 48**
Systematic review of effectiveness of different treatments for childhood retinoblastoma.
By McDaid C, Hartley S, Bagnall A-M, Ritchie G, Light K, Riemsma R.

**No. 49**
Towards evidence-based guidelines for the prevention of venous thromboembolism: systematic reviews of mechanical methods, oral anticoagulation, dextran and regional anaesthesia as thromboprophylaxis.
By Roderick P, Ferris G, Wilson K, Halls H, Jackson D, Collins R, *et al*.

**No. 50**
The effectiveness and cost-effectiveness of parent training/education programmes for the treatment of conduct disorder, including oppositional defiant disorder, in children.
By Dretzke J, Frew E, Davenport C, Barlow J, Stewart-Brown S, Sandercock J, *et al*.

## Volume 10, 2006

**No. 1**
The clinical and cost-effectiveness of donepezil, rivastigmine, galantamine and memantine for Alzheimer's disease.
By Loveman E, Green C, Kirby J, Takeda A, Picot J, Payne E, *et al*.

**No. 2**
FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke.
By Dennis M, Lewis S, Cranswick G, Forbes J.

**No. 3**
The clinical effectiveness and cost-effectiveness of computed tomography screening for lung cancer: systematic reviews.
By Black C, Bagust A, Boland A, Walker S, McLeod C, De Verteuil R, *et al*.

**No. 4**
A systematic review of the effectiveness and cost-effectiveness of neuroimaging assessments used to visualise the seizure focus in people with refractory epilepsy being considered for surgery.
By Whiting P, Gupta R, Burch J, Mujica Mota RE, Wright K, Marson A, *et al*.

**No. 5**
Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies.
By Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR.

**No. 6**
Systematic review and evaluation of methods of assessing urinary incontinence.
By Martin JL, Williams KS, Abrams KR, Turner DA, Sutton AJ, Chapple C, *et al*.

**No. 7**
The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review.
By Connock M, Frew E, Evans B-W, Bryan S, Cummins C, Fry-Smith A, *et al*.

**No. 8**
Surveillance of Barrett's oesophagus: exploring the uncertainty through systematic review, expert workshop and economic modelling.
By Garside R, Pitt M, Somerville M, Stein K, Price A, Gilbert N.

**No. 9**
Topotecan, pegylated liposomal doxorubicin hydrochloride and paclitaxel for second-line or subsequent treatment of advanced ovarian cancer: a systematic review and economic evaluation.
By Main C, Bojke L, Griffin S, Norman G, Barbieri M, Mather L, *et al*.

**No. 10**
Evaluation of molecular techniques in prediction and diagnosis of cytomegalovirus disease in immunocompromised patients.
By Szczepura A, Westmoreland D, Vinogradova Y, Fox J, Clark M.

**No. 11**
Screening for thrombophilia in high-risk situations: systematic review and cost-effectiveness analysis. The Thrombosis: Risk and Economic Assessment of Thrombophilia Screening (TREATS) study.
By Wu O, Robertson L, Twaddle S, Lowe GDO, Clark P, Greaves M, *et al*.

**No. 12**
A series of systematic reviews to inform a decision analysis for sampling and treating infected diabetic foot ulcers.
By Nelson EA, O'Meara S, Craig D, Iglesias C, Golder S, Dalton J, *et al*.

**No. 13**
Randomised clinical trial, observational study and assessment of cost-effectiveness of the treatment of varicose veins (REACTIV trial).
By Michaels JA, Campbell WB, Brazier JE, MacIntyre JB, Palfreyman SJ, Ratcliffe J, *et al*.

**No. 14**
The cost-effectiveness of screening for oral cancer in primary care.
By Speight PM, Palmer S, Moles DR, Downer MC, Smith DH, Henriksson M, *et al*.

**No. 15**
Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis.
By Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*.

**No. 16**
Systematic review of the effectiveness and cost-effectiveness of HealOzone® for the treatment of occlusal pit/fissure caries and root caries.
By Brazzelli M, McKenzie L, Fielding S, Fraser C, Clarkson J, Kilonzo M, *et al*.

**No. 17**
Randomised controlled trials of conventional antipsychotic versus new atypical drugs, and new atypical drugs versus clozapine, in people with schizophrenia responding poorly to, or intolerant of, current drug treatment.
By Lewis SW, Davies L, Jones PB, Barnes TRE, Murray RM, Kerwin R, *et al*.

**No. 18**
Diagnostic tests and algorithms used in the investigation of haematuria: systematic reviews and economic evaluation.
By Rodgers M, Nixon J, Hempel S, Aho T, Kelly J, Neal D, *et al*.

**No. 19**
Cognitive behavioural therapy in addition to antispasmodic therapy for irritable bowel syndrome in primary care: randomised controlled trial.
By Kennedy TM, Chalder T, McCrone P, Darnley S, Knapp M, Jones RH, *et al*.

**No. 20**
A systematic review of the clinical effectiveness and cost-effectiveness of enzyme replacement therapies for Fabry's disease and mucopolysaccharidosis type 1.
By Connock M, Juarez-Garcia A, Frew E, Mans A, Dretzke J, Fry-Smith A, *et al*.

**No. 21**
Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation.
By Wright M, Grieve R, Roberts J, Main J, Thomas HC, on behalf of the UK Mild Hepatitis C Trial Investigators.

**No. 22**
Pressure relieving support surfaces: a randomised evaluation.
By Nixon J, Nelson EA, Cranny G, Iglesias CP, Hawkins K, Cullum NA, *et al*.

**No. 23**
A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents.
By King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, *et al.*

**No. 24**
The clinical effectiveness and cost-effectiveness of enzyme replacement therapy for Gaucher's disease: a systematic review.
By Connock M, Burls A, Frew E, Fry-Smith A, Juarez-Garcia A, McCabe C, *et al*.

**No. 25**
Effectiveness and cost-effectiveness of salicylic acid and cryotherapy for cutaneous warts. An economic decision model.
By Thomas KS, Keogh-Brown MR, Chalmers JR, Fordham RJ, Holland RC, Armstrong SJ, *et al*.

**No. 26**
A systematic literature review of the effectiveness of non-pharmacological interventions to prevent wandering in dementia and evaluation of the ethical implications and acceptability of their use.
By Robinson L, Hutchings D, Corner L, Beyer F, Dickinson H, Vanoli A, *et al*.

**No. 27**
A review of the evidence on the effects and costs of implantable cardioverter defibrillator therapy in different patient groups, and modelling of cost-effectiveness and cost–utility for these groups in a UK context.
By Buxton M, Caine N, Chase D, Connelly D, Grace A, Jackson C, *et al*.

**No. 28**
Adefovir dipivoxil and pegylated interferon alfa-2a for the treatment of chronic hepatitis B: a systematic review and economic evaluation.
By Shepherd J, Jones J, Takeda A, Davidson P, Price A.

**No. 29**
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.
By Harvey S, Stevens K, Harrison D, Young D, Brampton W, McCabe C, *et al*.

**No. 30**
Accurate, practical and cost-effective assessment of carotid stenosis in the UK.
By Wardlaw JM, Chappell FM, Stevenson M, De Nigris E, Thomas S, Gillard J, *et al*.

**No. 31**
Etanercept and infliximab for the treatment of psoriatic arthritis: a systematic review and economic evaluation.
By Woolacott N, Bravo Vergel Y, Hawkins N, Kainth A, Khadjesari Z, Misso K, *et al*.

**No. 32**
The cost-effectiveness of testing for hepatitis C in former injecting drug users.
By Castelnuovo E, Thompson-Coon J, Pitt M, Cramp M, Siebert U, Price A, *et al*.

**No. 33**
Computerised cognitive behaviour therapy for depression and anxiety update: a systematic review and economic evaluation.
By Kaltenthaler E, Brazier J, De Nigris E, Tumur I, Ferriter M, Beverley C, *et al*.

**No. 34**
Cost-effectiveness of using prognostic information to select women with breast cancer for adjuvant systemic therapy.
By Williams C, Brunskill S, Altman D, Briggs A, Campbell H, Clarke M, *et al*.

**No. 35**
Psychological therapies including dialectical behaviour therapy for borderline personality disorder: a systematic review and preliminary economic evaluation.
By Brazier J, Tumur I, Holmes M, Ferriter M, Parry G, Dent-Brown K, *et al*.

**No. 36**
Clinical effectiveness and cost-effectiveness of tests for the diagnosis and investigation of urinary tract infection in children: a systematic review and economic model.
By Whiting P, Westwood M, Bojke L, Palmer S, Richardson G, Cooper J, *et al*.

**No. 37**
Cognitive behavioural therapy in chronic fatigue syndrome: a randomised controlled trial of an outpatient group programme.
By O'Dowd H, Gladwell P, Rogers CA, Hollinghurst S, Gregory A.

**No. 38**
A comparison of the cost-effectiveness of five strategies for the prevention of nonsteroidal anti-inflammatory drug-induced gastrointestinal toxicity: a systematic review with economic modelling.
By Brown TJ, Hooper L, Elliott RA, Payne K, Webb R, Roberts C, et al.

**No. 39**
The effectiveness and cost-effectiveness of computed tomography screening for coronary artery disease: systematic review.
By Waugh N, Black C, Walker S, McIntyre L, Cummins E, Hillis G.

**No. 40**
What are the clinical outcome and cost-effectiveness of endoscopy undertaken by nurses when compared with doctors? A Multi-Institution Nurse Endoscopy Trial (MINuET).
By Williams J, Russell I, Durai D, Cheung W-Y, Farrin A, Bloor K, *et al*.

**No. 41**
The clinical and cost-effectiveness of oxaliplatin and capecitabine for the adjuvant treatment of colon cancer: systematic review and economic evaluation.
By Pandor A, Eggington S, Paisley S, Tappenden P, Sutcliffe P.

**No. 42**
A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness.
By Chen Y-F, Jobanputra P, Barton P, Jowett S, Bryan S, Clark W, *et al*.

**No. 43**
Telemedicine in dermatology: a randomised controlled trial.
By Bowns IR, Collins K, Walters SJ, McDonagh AJG.

**No. 44**
Cost-effectiveness of cell salvage and alternative methods of minimising perioperative allogeneic blood transfusion: a systematic review and economic model.
By Davies L, Brown TJ, Haynes S, Payne K, Elliott RA, McCollum C.

**No. 45**
Clinical effectiveness and cost-effectiveness of laparoscopic surgery for colorectal cancer: systematic reviews and economic evaluation.
By Murray A, Lourenco T, de Verteuil R, Hernandez R, Fraser C, McKinley A, *et al*.

**No. 46**
Etanercept and efalizumab for the treatment of psoriasis: a systematic review.
By Woolacott N, Hawkins N, Mason A, Kainth A, Khadjesari Z, Bravo Vergel Y, *et al*.

**No. 47**
Systematic reviews of clinical decision tools for acute abdominal pain.
By Liu JLY, Wyatt JC, Deeks JJ, Clamp S, Keen J, Verde P, *et al*.

**No. 48**
Evaluation of the ventricular assist device programme in the UK.
By Sharples L, Buxton M, Caine N, Cafferty F, Demiris N, Dyer M, *et al*.

**No. 49**
A systematic review and economic model of the clinical and cost-effectiveness of immunosuppressive therapy for renal transplantation in children.
By Yao G, Albon E, Adi Y, Milford D, Bayliss S, Ready A, *et al*.

**No. 50**
Amniocentesis results: investigation of anxiety. The ARIA trial.
By Hewison J, Nixon J, Fountain J, Cocks K, Jones C, Mason G, *et al*.

## Volume 11, 2007

**No. 1**
Pemetrexed disodium for the treatment of malignant pleural mesothelioma: a systematic review and economic evaluation.
By Dundar Y, Bagust A, Dickson R, Dodd S, Green J, Haycox A, *et al*.

**No. 2**
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of docetaxel in combination with prednisone or prednisolone for the treatment of hormone-refractory metastatic prostate cancer.
By Collins R, Fenwick E, Trowman R, Perard R, Norman G, Light K, *et al*.

**No. 3**
A systematic review of rapid diagnostic tests for the detection of tuberculosis infection.
By Dinnes J, Deeks J, Kunst H, Gibson A, Cummins E, Waugh N, *et al*.

**No. 4**
The clinical effectiveness and cost-effectiveness of strontium ranelate for the prevention of osteoporotic fragility fractures in postmenopausal women.
By Stevenson M, Davis S, Lloyd-Jones M, Beverley C.

**No. 5**
A systematic review of quantitative and qualitative research on the role and effectiveness of written information available to patients about individual medicines.
By Raynor DK, Blenkinsopp A, Knapp P, Grime J, Nicolson DJ, Pollock K, *et al*.

**No. 6**
Oral naltrexone as a treatment for relapse prevention in formerly opioid-dependent drug users: a systematic review and economic evaluation.
By Adi Y, Juarez-Garcia A, Wang D, Jowett S, Frew E, Day E, *et al*.

**No. 7**
Glucocorticoid-induced osteoporosis: a systematic review and cost–utility analysis.
By Kanis JA, Stevenson M, McCloskey EV, Davis S, Lloyd-Jones M.

**No. 8**
Epidemiological, social, diagnostic and economic evaluation of population screening for genital chlamydial infection.
By Low N, McCarthy A, Macleod J, Salisbury C, Campbell R, Roberts TE, *et al*.

**No. 9**
Methadone and buprenorphine for the management of opioid dependence: a systematic review and economic evaluation.
By Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, *et al*.

**No. 10**
Exercise Evaluation Randomised Trial (EXERT): a randomised trial comparing GP referral for leisure centre-based exercise, community-based walking and advice only.
By Isaacs AJ, Critchley JA, See Tai S, Buckingham K, Westley D, Harridge SDR, *et al*.

**No. 11**
Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation.
By Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N.

**No. 12**
Systematic review and economic evaluation of bevacizumab and cetuximab for the treatment of metastatic colorectal cancer.
By Tappenden P, Jones R, Paisley S, Carroll C.

**No. 13**
A systematic review and economic evaluation of epoetin alfa, epoetin beta and darbepoetin alfa in anaemia associated with cancer, especially that attributable to cancer treatment.
By Wilson J, Yao GL, Raftery J, Bohlius J, Brunskill S, Sandercock J, *et al*.

**No. 14**
A systematic review and economic evaluation of statins for the prevention of coronary events.
By Ward S, Lloyd Jones M, Pandor A, Holmes M, Ara R, Ryan A, *et al*.

**No. 15**
A systematic review of the effectiveness and cost-effectiveness of different models of community-based respite care for frail older people and their carers.
By Mason A, Weatherly H, Spilsbury K, Arksey H, Golder S, Adamson J, *et al*.

**No. 16**
Additional therapy for young children with spastic cerebral palsy: a randomised controlled trial.
By Weindling AM, Cunningham CC, Glenn SM, Edwards RT, Reeves DJ.

**No. 17**
Screening for type 2 diabetes: literature review and economic modelling.
By Waugh N, Scotland G, McNamee P, Gillett M, Brennan A, Goyder E, *et al*.

**No. 18**
The effectiveness and cost-effectiveness of cinacalcet for secondary hyperparathyroidism in end-stage renal disease patients on dialysis: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Mealing S, Roome C, Snaith A, *et al*.

**No. 19**
The clinical effectiveness and cost-effectiveness of gemcitabine for metastatic breast cancer: a systematic review and economic evaluation.
By Takeda AL, Jones J, Loveman E, Tan SC, Clegg AJ.

**No. 20**
A systematic review of duplex ultrasound, magnetic resonance angiography and computed tomography angiography for the diagnosis and assessment of symptomatic, lower limb peripheral arterial disease.
By Collins R, Cranny G, Burch J, Aguiar-Ibáñez R, Craig D, Wright K, *et al*.

**No. 21**
The clinical effectiveness and cost-effectiveness of treatments for children with idiopathic steroid-resistant nephrotic syndrome: a systematic review.
By Colquitt JL, Kirby J, Green C, Cooper K, Trompeter RS.

**No. 22**
A systematic review of the routine monitoring of growth in children of primary school age to identify growth-related conditions.
By Fayter D, Nixon J, Hartley S, Rithalia A, Butler G, Rudolf M, *et al*.

**No. 23**
Systematic review of the effectiveness of preventing and treating *Staphylococcus aureus* carriage in reducing peritoneal catheter-related infections.
By McCormack K, Rabindranath K, Kilonzo M, Vale L, Fraser C, McIntyre L, *et al*.

**No. 24**
The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis.
By McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, *et al*.

**No. 25**
A randomised controlled trial and economic evaluation of direct versus indirect and individual versus group modes of speech and language therapy for children with primary language impairment.
By Boyle J, McCartney E, Forbes J, O'Hare A.

**No. 26**
Hormonal therapies for early breast cancer: systematic review and economic evaluation.
By Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L.

**No. 27**
Cardioprotection against the toxic effects of anthracyclines given to children with cancer: a systematic review.
By Bryant J, Picot J, Levitt G, Sullivan I, Baxter L, Clegg A.

**No. 28**
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis: a systematic review and economic evaluation.
By McLeod C, Bagust A, Boland A, Dagenais P, Dickson R, Dundar Y, *et al*.

**No. 29**
Prenatal screening and treatment strategies to prevent group B streptococcal and other bacterial infections in early infancy: cost-effectiveness and expected value of information analyses.
By Colbourn T, Asseburg C, Bojke L, Philips Z, Claxton K, Ades AE, *et al*.

**No. 30**
Clinical effectiveness and cost-effectiveness of bone morphogenetic proteins in the non-healing of fractures and spinal fusion: a systematic review.
By Garrison KR, Donell S, Ryder J, Shemilt I, Mugford M, Harvey I, *et al*.

**No. 31**
A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial.
By Prescott RJ, Kunkler IH, Williams LJ, King CC, Jack W, van der Pol M, *et al*.

**No. 32**
Current practice, accuracy, effectiveness and cost-effectiveness of the school entry hearing screen.
By Bamford J, Fortnum H, Bristow K, Smith J, Vamvakas G, Davies L, *et al*.

**No. 33**
The clinical effectiveness and cost-effectiveness of inhaled insulin in diabetes mellitus: a systematic review and economic evaluation.
By Black C, Cummins E, Royle P, Philip S, Waugh N.

**No. 34**
Surveillance of cirrhosis for hepatocellular carcinoma: systematic review and economic analysis.
By Thompson Coon J, Rogers G, Hewson P, Wright D, Anderson R, Cramp M, *et al*.

**No. 35**
The Birmingham Rehabilitation Uptake Maximisation Study (BRUM). Homebased compared with hospital-based cardiac rehabilitation in a multi-ethnic population: cost-effectiveness and patient adherence.
By Jolly K, Taylor R, Lip GYH, Greenfield S, Raftery J, Mant J, *et al*.

**No. 36**
A systematic review of the clinical, public health and cost-effectiveness of rapid diagnostic tests for the detection and identification of bacterial intestinal pathogens in faeces and food.
By Abubakar I, Irvine L, Aldus CF, Wyatt GM, Fordham R, Schelenz S, *et al*.

**No. 37**
A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial.
By Marson AG, Appleton R, Baker GA, Chadwick DW, Doughty J, Eaton B, *et al*.

**No. 38**
Clinical effectiveness and cost-effectiveness of different models of managing long-term oral anti-coagulation therapy: a systematic review and economic modelling.
By Connock M, Stevens C, Fry-Smith A, Jowett S, Fitzmaurice D, Moore D, *et al*.

**No. 39**
A systematic review and economic model of the clinical effectiveness and cost-effectiveness of interventions for preventing relapse in people with bipolar disorder.
By Soares-Weiser K, Bravo Vergel Y, Beynon S, Dunn G, Barbieri M, Duffy S, *et al*.

**No. 40**
Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation.
By Ward S, Simpson E, Davis S, Hind D, Rees A, Wilkinson A.

**No. 41**
The clinical effectiveness and cost-effectiveness of screening for open angle glaucoma: a systematic review and economic evaluation.
By Burr JM, Mowatt G, Hernández R, Siddiqui MAR, Cook J, Lourenco T, *et al*.

**No. 42**
Acceptability, benefit and costs of early screening for hearing disability: a study of potential screening tests and models.
By Davis A, Smith P, Ferguson M, Stephens D, Gianopoulos I.

**No. 43**
Contamination in trials of educational interventions.
By Keogh-Brown MR, Bachmann MO, Shepstone L, Hewitt C, Howe A, Ramsay CR, *et al*.

**No. 44**
Overview of the clinical effectiveness of positron emission tomography imaging in selected cancers.
By Facey K, Bradbury I, Laking G, Payne E.

**No. 45**
The effectiveness and cost-effectiveness of carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma: a systematic review and economic evaluation.
By Garside R, Pitt M, Anderson R, Rogers G, Dyer M, Mealing S, *et al*.

**No. 46**
Drug-eluting stents: a systematic review and economic evaluation.
By Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, *et al*.

**No. 47**
The clinical effectiveness and cost-effectiveness of cardiac resynchronisation (biventricular pacing) for heart failure: systematic review and economic model.
By Fox M, Mealing S, Anderson R, Dean J, Stein K, Price A, *et al*.

**No. 48**
Recruitment to randomised trials: strategies for trial enrolment and participation study. The STEPS study.
By Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, *et al*.

**No. 49**
Cost-effectiveness of functional cardiac testing in the diagnosis and management of coronary artery disease: a randomised controlled trial. The CECaT trial.
By Sharples L, Hughes V, Crean A, Dyer M, Buxton M, Goldsmith K, *et al*.

**No. 50**
Evaluation of diagnostic tests when there is no gold standard. A review of methods.
By Rutjes AWS, Reitsma JB, Coomarasamy A, Khan KS, Bossuyt PMM.

**No. 51**
Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding.
By Leontiadis GI, Sreedharan A, Dorward S, Barton P, Delaney B, Howden CW, *et al*.

**No. 52**
A review and critique of modelling in prioritising and designing screening programmes.
By Karnon J, Goyder E, Tappenden P, McPhie S, Towers I, Brazier J, *et al*.

**No. 53**
An assessment of the impact of the NHS Health Technology Assessment Programme.
By Hanney S, Buxton M, Green C, Coulson D, Raftery J.

## Volume 12, 2008

**No. 1**
A systematic review and economic model of switching from nonglycopeptide to glycopeptide antibiotic prophylaxis for surgery.
By Cranny G, Elliott R, Weatherly H, Chambers D, Hawkins N, Myers L, *et al*.

**No. 2**
'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis.
By Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D.

**No. 3**
A systematic review of the effectiveness of strategies for reducing fracture risk in children with juvenile idiopathic arthritis with additional data on long-term risk of fracture and cost of disease management.
By Thornton J, Ashcroft D, O'Neill T, Elliott R, Adams J, Roberts C, *et al*.

**No. 4**
Does befriending by trained lay workers improve psychological well-being and quality of life for carers of people with dementia, and at what cost? A randomised controlled trial.
By Charlesworth G, Shepstone L, Wilson E, Thalanany M, Mugford M, Poland F.

**No. 5**
A multi-centre retrospective cohort study comparing the efficacy, safety and cost-effectiveness of hysterectomy and uterine artery embolisation for the treatment of symptomatic uterine fibroids. The HOPEFUL study.
By Hirst A, Dutton S, Wu O, Briggs A, Edwards C, Waldenmaier L, *et al*.

**No. 6**
Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling.
By Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, *et al*.

**No. 7**
The use of economic evaluations in NHS decision-making: a review and empirical investigation.
By Williams I, McIver S, Moore D, Bryan S.

**No. 8**
Stapled haemorrhoidectomy (haemorrhoidopexy) for the treatment of haemorrhoids: a systematic review and economic evaluation.
By Burch J, Epstein D, Baba-Akbari A, Weatherly H, Fox D, Golder S, *et al*.

**No. 9**
The clinical effectiveness of diabetes education models for Type 2 diabetes: a systematic review.
By Loveman E, Frampton GK, Clegg AJ.

**No. 10**
Payment to healthcare professionals for patient recruitment to trials: systematic review and qualitative study.
By Raftery J, Bryant J, Powell J, Kerr C, Hawker S.

**No. 11**
Cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs (etodolac, meloxicam, celecoxib, rofecoxib, etoricoxib, valdecoxib and lumiracoxib) for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation.
By Chen Y-F, Jobanputra P, Barton P, Bryan S, Fry-Smith A, Harris G, *et al*.

**No. 12**
The clinical effectiveness and cost-effectiveness of central venous catheters treated with anti-infective agents in preventing bloodstream infections: a systematic review and economic evaluation.
By Hockenhull JC, Dwan K, Boland A, Smith G, Bagust A, Dundar Y, *et al*.

**No. 13**
Stepped treatment of older adults on laxatives. The STOOL trial.
By Mihaylov S, Stark C, McColl E, Steen N, Vanoli A, Rubin G, *et al*.

**No. 14**
A randomised controlled trial of cognitive behaviour therapy in adolescents with major depression treated by selective serotonin reuptake inhibitors. The ADAPT trial.
By Goodyer IM, Dubicka B, Wilkinson P, Kelvin R, Roberts C, Byford S, *et al*.

**No. 15**
The use of irinotecan, oxaliplatin and raltitrexed for the treatment of advanced colorectal cancer: systematic review and economic evaluation.
By Hind D, Tappenden P, Tumur I, Eggington E, Sutcliffe P, Ryan A.

**No. 16**
Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation.
By Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A.

**No. 17**
Systematic review of the clinical effectiveness and cost-effectiveness of 64-slice or higher computed tomography angiography as an alternative to invasive coronary angiography in the investigation of coronary artery disease.
By Mowatt G, Cummins E, Waugh N, Walker S, Cook J, Jia X, *et al*.

**No. 18**
Structural neuroimaging in psychosis: a systematic review and economic evaluation.
By Albon E, Tsourapas A, Frew E, Davenport C, Oyebode F, Bayliss S, *et al*.

**No. 19**
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in adults and children aged 12 years and over.
By Shepherd J, Rogers G, Anderson R, Main C, Thompson-Coon J, Hartwell D, *et al*.

**No. 20**
Systematic review and economic analysis of the comparative effectiveness of different inhaled corticosteroids and their usage with long-acting beta$_2$ agonists for the treatment of chronic asthma in children under the age of 12 years.
By Main C, Shepherd J, Anderson R, Rogers G, Thompson-Coon J, Liu Z, *et al*.

**No. 21**
Ezetimibe for the treatment of hypercholesterolaemia: a systematic review and economic evaluation.
By Ara R, Tumur I, Pandor A, Duenas A, Williams R, Wilkinson A, *et al*.

**No. 22**
Topical or oral ibuprofen for chronic knee pain in older people. The TOIB study.
By Underwood M, Ashby D, Carnes D, Castelnuovo E, Cross P, Harding G, *et al*.

**No. 23**
A prospective randomised comparison of minor surgery in primary and secondary care. The MiSTIC trial.
By George S, Pockney P, Primrose J, Smith H, Little P, Kinley H, *et al*.

**No. 24**
A review and critical appraisal of measures of therapist–patient interactions in mental health settings.
By Cahill J, Barkham M, Hardy G, Gilbody S, Richards D, Bower P, *et al*.

**No. 25**
The clinical effectiveness and cost-effectiveness of screening programmes for amblyopia and strabismus in children up to the age of 4–5 years: a systematic review and economic evaluation.
By Carlton J, Karnon J, Czoski-Murray C, Smith KJ, Marr J.

**No. 26**
A systematic review of the clinical effectiveness and cost-effectiveness and economic modelling of minimal incision total hip replacement approaches in the management of arthritic disease of the hip.
By de Verteuil R, Imamura M, Zhu S, Glazener C, Fraser C, Munro N, *et al*.

**No. 27**
A preliminary model-based assessment of the cost–utility of a screening programme for early age-related macular degeneration.
By Karnon J, Czoski-Murray C, Smith K, Brand C, Chakravarthy U, Davis S, *et al*.

**No. 28**
Intravenous magnesium sulphate and sotalol for prevention of atrial fibrillation after coronary artery bypass surgery: a systematic review and economic evaluation.
By Shepherd J, Jones J, Frampton GK, Tanajewski L, Turner D, Price A.

**No. 29**
Absorbent products for urinary/faecal incontinence: a comparative evaluation of key product categories.
By Fader M, Cottenden A, Getliffe K, Gage H, Clarke-O'Neill S, Jamieson K, *et al*.

**No. 30**
A systematic review of repetitive functional task practice with modelling of resource use, costs and effectiveness.
By French B, Leathley M, Sutton C, McAdam J, Thomas L, Forster A, *et al*.

**No. 31**
The effectiveness and cost-effectivness of minimal access surgery amongst people with gastro-oesophageal reflux disease – a UK collaborative study. The REFLUX trial.
By Grant A, Wileman S, Ramsay C, Bojke L, Epstein D, Sculpher M, *et al*.

**No. 32**
Time to full publication of studies of anti-cancer medicines for breast cancer and the potential for publication bias: a short systematic review.
By Takeda A, Loveman E, Harris P, Hartwell D, Welch K.

**No. 33**
Performance of screening tests for child physical abuse in accident and emergency departments.
By Woodman J, Pitt M, Wentz R, Taylor B, Hodes D, Gilbert RE.

**No. 34**
Curative catheter ablation in atrial fibrillation and typical atrial flutter: systematic review and economic evaluation.
By Rodgers M, McKenna C, Palmer S, Chambers D, Van Hout S, Golder S, *et al*.

**No. 35**
Systematic review and economic modelling of effectiveness and cost utility of surgical treatments for men with benign prostatic enlargement.
By Lourenco T, Armstrong N, N'Dow J, Nabi G, Deverill M, Pickard R, *et al*.

**No. 36**
Immunoprophylaxis against respiratory syncytial virus (RSV) with palivizumab in children: a systematic review and economic evaluation.
By Wang D, Cummins C, Bayliss S, Sandercock J, Burls A.

**Volume 13, 2009**

**No. 1**
Deferasirox for the treatment of iron overload associated with regular blood transfusions (transfusional haemosiderosis) in patients suffering with chronic anaemia: a systematic review and economic evaluation.
By McLeod C, Fleeman N, Kirkham J, Bagust A, Boland A, Chu P, *et al*.

**No. 2**
Thrombophilia testing in people with venous thromboembolism: systematic review and cost-effectiveness analysis.
By Simpson EL, Stevenson MD, Rawdin A, Papaioannou D.

**No. 3**
Surgical procedures and non-surgical devices for the management of non-apnoeic snoring: a systematic review of clinical effects and associated treatment costs.
By Main C, Liu Z, Welch K, Weiner G, Quentin Jones S, Stein K.

**No. 4**
Continuous positive airway pressure devices for the treatment of obstructive sleep apnoea–hypopnoea syndrome: a systematic review and economic analysis.
By McDaid C, Griffin S, Weatherly H, Durée K, van der Burgt M, van Hout S, Akers J, *et al*.

**No. 5**
Use of classical and novel biomarkers as prognostic risk factors for localised prostate cancer: a systematic review.
By Sutcliffe P, Hummel S, Simpson E, Young T, Rees A, Wilkinson A, *et al*.

**No. 6**
The harmful health effects of recreational ecstasy: a systematic review of observational evidence.
By Rogers G, Elston J, Garside R, Roome C, Taylor R, Younger P, *et al*.

# Health Technology Assessment Programme



## Prioritisation Strategy Group

**Members**



## HTA Commissioning Board

**Members**



**Observers**

# Diagnostic Technologies & Screening Panel

**Members**

**Chair,**
**Professor Paul Glasziou,**
Professor of Evidence-Based Medicine, University of Oxford

**Deputy Chair,**
**Dr David Elliman,**
Consultant Paediatrician and Honorary Senior Lecturer, Great Ormond Street Hospital, London

Professor Judith E Adams, Consultant Radiologist, Manchester Royal Infirmary, Central Manchester & Manchester Children's University Hospitals NHS Trust, and Professor of Diagnostic Radiology, Imaging Science and Biomedical Engineering, Cancer & Imaging Sciences, University of Manchester

Ms Jane Bates, Consultant Ultrasound Practitioner, Ultrasound Department, Leeds Teaching Hospital NHS Trust

Dr Stephanie Dancer, Consultant Microbiologist, Hairmyres Hospital, East Kilbride

Professor Glyn Elwyn, Primary Medical Care Research Group, Swansea Clinical School, University of Wales

Dr Ron Gray, Consultant Clinical Epidemiologist, Department of Public Health, University of Oxford

Professor Paul D Griffiths, Professor of Radiology, University of Sheffield

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Medical Director, Medicines & Healthcare Products Regulatory Agency, London

Dr Anne Mackie, Director of Programmes, UK National Screening Committee

Dr Michael Millar, Consultant Senior Lecturer in Microbiology, Barts and The London NHS Trust, Royal London Hospital

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative

Dr Phil Shackley, Senior Lecturer in Health Economics, School of Population and Health Sciences, University of Newcastle upon Tyne

Dr W Stuart A Smellie, Consultant in Chemical Pathology, Bishop Auckland General Hospital

Dr Nicholas Summerton, Consultant Clinical and Public Health Advisor, NICE

Ms Dawn Talbot, Service User Representative

Dr Graham Taylor, Scientific Advisor, Regional DNA Laboratory, St James's University Hospital, Leeds

Professor Lindsay Wilson Turnbull, Scientific Director of the Centre for Magnetic Resonance Investigations and YCR Professor of Radiology, Hull Royal Infirmary

**Observers**

Dr Tim Elliott, Team Leader, Cancer Screening, Department of Health

Dr Catherine Moody, Programme Manager, Neuroscience and Mental Health Board

Dr Ursula Wells, Principal Research Officer, Department of Health

# Pharmaceuticals Panel

**Members**

**Chair,**
**Professor Robin Ferner,**
Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

**Deputy Chair,**
**Professor Imti Choonara,**
Professor in Child Health, University of Nottingham

Mrs Nicola Carey, Senior Research Fellow, School of Health and Social Care, The University of Reading

Mr John Chapman, Service User Representative

Dr Peter Elton, Director of Public Health, Bury Primary Care Trust

Dr Ben Goldacre, Research Fellow, Division of Psychological Medicine and Psychiatry, King's College London

Mrs Barbara Greggains, Service User Representative

Dr Bill Gutteridge, Medical Adviser, London Strategic Health Authority

Dr Dyfrig Hughes, Reader in Pharmacoeconomics and Deputy Director, Centre for Economics and Policy in Health, IMSCaR, Bangor University

Professor Jonathan Ledermann, Professor of Medical Oncology and Director of the Cancer Research UK and University College London Cancer Trials Centre

Dr Yoon K Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Professor Femi Oyebode, Consultant Psychiatrist and Head of Department, University of Birmingham

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician and Gynaecologist, The Rosie Hospital, University of Cambridge

Dr Martin Shelly, General Practitioner, Leeds, and Associate Director, NHS Clinical Governance Support Team, Leicester

Dr Gillian Shepherd, Director, Health and Clinical Excellence, Merck Serono Ltd

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Mr David Symes, Service User Representative

Dr Lesley Wise, Unit Manager, Pharmacoepidemiology Research Unit, VRMM, Medicines & Healthcare Products Regulatory Agency

**Observers**

Ms Kay Pattison, Section Head, NHS R&D Programme, Department of Health

Mr Simon Reeve, Head of Clinical and Cost-Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health

Dr Heike Weber, Programme Manager, Medical Research Council

Dr Ursula Wells, Principal Research Officer, Department of Health



Current and past membership details of all HTA Programme 'committees' are available from the HTA website (www.hta.ac.uk)

# Therapeutic Procedures Panel

**Members**

**Chair,**
**Dr John C Pounsford,**
Consultant Physician, North Bristol NHS Trust

**Deputy Chair,**
**Professor Scott Weich,**
Professor of Psychiatry, Division of Health in the Community, University of Warwick, Coventry

Professor Jane Barlow,
Professor of Public Health in the Early Years, Health Sciences Research Institute, Warwick Medical School, Coventry

Ms Maree Barnett,
Acting Branch Head of Vascular Programme, Department of Health

Mrs Val Carlill,
Service User Representative

Mrs Anthea De Barton-Watson,
Service User Representative

Mr Mark Emberton,
Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital, London

Professor Steve Goodacre,
Professor of Emergency Medicine, University of Sheffield

Professor Christopher Griffiths,
Professor of Primary Care, Barts and The London School of Medicine and Dentistry

Mr Paul Hilton,
Consultant Gynaecologist and Urogynaecologist, Royal Victoria Infirmary, Newcastle upon Tyne

Professor Nicholas James,
Professor of Clinical Oncology, University of Birmingham, and Consultant in Clinical Oncology, Queen Elizabeth Hospital

Dr Peter Martin,
Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Dr Kate Radford,
Senior Lecturer (Research), Clinical Practice Research Unit, University of Central Lancashire, Preston

Mr Jim Reece
Service User Representative

Dr Karen Roberts,
Nurse Consultant, Dunston Hill Hospital Cottages

**Observers**

Dr Phillip Leech,
Principal Medical Officer for Primary Care, Department of Health

Ms Kay Pattison,
Section Head, NHS R&D Programme, Department of Health

Dr Morven Roberts,
Clinical Trials Manager, Medical Research Council

Professor Tom Walley,
Director, NIHR HTA Programme, Professor of Clinical Pharmacology, University of Liverpool

Dr Ursula Wells,
Principal Research Officer, Department of Health

# Disease Prevention Panel

**Members**

**Chair,**
**Dr Edmund Jessop,**
Medical Adviser, National Specialist, National Commissioning Group (NCG), London

**Deputy Chair,**
**Dr David Pencheon,**
Director, NHS Sustainable Development Unit, Cambridge

Dr Elizabeth Fellow-Smith,
Medical Director, West London Mental Health Trust, Middlesex

Dr John Jackson,
General Practitioner, Parkway Medical Centre, Newcastle upon Tyne

Professor Mike Kelly,
Director, Centre for Public Health Excellence, NICE, London

Dr Chris McCall,
General Practitioner, The Hadleigh Practice, Corfe Mullen, Dorset

Ms Jeanett Martin,
Director of Nursing, BarnDoc Limited, Lewisham Primary Care Trust

Dr Julie Mytton,
Locum Consultant in Public Health Medicine, Bristol Primary Care Trust

Miss Nicky Mullany,
Service User Representative

Professor Ian Roberts,
Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine

Professor Ken Stein,
Senior Clinical Lecturer in Public Health, University of Exeter

Dr Kieran Sweeney,
Honorary Clinical Senior Lecturer, Peninsula College of Medicine and Dentistry, Universities of Exeter and Plymouth

Professor Carol Tannahill,
Glasgow Centre for Population Health

Professor Margaret Thorogood,
Professor of Epidemiology, University of Warwick Medical School, Coventry

**Observers**

Ms Christine McGuire,
Research & Development, Department of Health

Dr Caroline Stone,
Programme Manager, Medical Research Council

# Expert Advisory Network

**Members**

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Professor of Social Gerontology & Health Services Research, University of Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer and Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing and Head of Research, The Medical School, University of Birmingham

Professor Barry Cookson, Director, Laboratory of Hospital Infection, Public Health Laboratory Service, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, Institute of Child Health, London

Mr John Dunning, Consultant Cardiothoracic Surgeon, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Dean of Faculty of Medicine, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts and The London School of Medicine and Dentistry

Mr Leonard R Fenwick, Chief Executive, Freeman Hospital, Newcastle upon Tyne

Mrs Gillian Fletcher, Antenatal Teacher and Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, University of Birmingham

Mr Tam Fry, Honorary Chairman, Child Growth Foundation, London

Professor Fiona Gilbert, Consultant Radiologist and NCRN Member, University of Aberdeen

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, South Tees Hospital NHS Trust

Bec Hanley, Co-director, TwoCan Associates, West Sussex

Dr Maryann L Hardy, Senior Lecturer, University of Bradford

Mrs Sharon Hart, Healthcare Management Consultant, Reading

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Richard Hobbs, Head of Department of Primary Care & General Practice, University of Birmingham

Professor Alan Horwich, Dean and Section Chairman, The Institute of Cancer Research, London

Professor Allen Hutchinson, Director of Public Health and Deputy Dean of ScHARR, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Royal Marsden Hospital and Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director and Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester

Professor Julian Little, Professor of Human Genome Epidemiology, University of Ottawa

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Professor Rajan Madhok, Medical Director and Director of Public Health, Directorate of Clinical Strategy & Public Health, North & East Yorkshire & Northern Lincolnshire Health Authority, York

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Professor Miranda Mugford, Professor of Health Economics and Group Co-ordinator, University of East Anglia

Professor Jim Neilson, Head of School of Reproductive & Developmental Medicine and Professor of Obstetrics and Gynaecology, University of Liverpool

Mrs Julietta Patnick, National Co-ordinator, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Director of Clinical Research, Bayer Diagnostics Europe, Stoke Poges

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon Primary Care Trust, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, St James's University Hospital, Leeds

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Professor Sarah Stewart-Brown, Professor of Public Health, Division of Health in the Community, University of Warwick, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick, Coventry

Mrs Joan Webster, Consumer Member, Southern Derbyshire Community Health Council

Professor Martin Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Children's Health, Lymington

## Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

***We look forward to hearing from you.***

The NIHR Coordinating Centre for Health Technology Assessment
Alpha House, Enterprise Road
Southampton Science Park
Chilworth
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

ISSN 1366-5278