Report methods for assessing the outcomes arising from the use of the interventions

The systematic review of clinical effectiveness will adhere to standard methodology as outlined in the CRD guidance for undertaking reviews in health care.

Population

The relevant study population for this assessment is patients receiving GA for surgery, including adults and children in whom the technology is licensed. Elderly and obese patients undergoing GA will be included as sub-groups for this evaluation where data allow.

Studies of patients receiving sedation in settings such as intensive care or high-dependency units are not relevant to this assessment. Studies of anaesthesia monitoring in healthy volunteers, or in non-surgical anaesthesia will not be included. Studies in which only regional or local anaesthesia are given will not be included.

Interventions

- E-Entropy.
- BIS.
- Narcotrend.

Comparators

The comparator in this assessment is standard clinical observation, including one or more of the following clinical markers: end-tidal anaesthetic gas concentrations (for inhaled anaesthesia); pulse measurement; heart rhythm; blood pressure; lacrimation; and sweating.

Outcomes

Studies will be included if they report one or more of the following outcomes:

- probability of intraoperative awareness
- patient distress and other sequelae resulting from intraoperative awareness
- recovery status (e.g. Aldrete scoring system)
- time to emergence from anaesthesia
- time to extubation (if appropriate)
- time to discharge from the recovery room
- consumption of anaesthetic agents
- morbidity and mortality including postoperative cognitive dysfunction from anaesthetic agents, pain-relieving drugs, antibiotics, antisickness drugs and muscle relaxants
- HRQoL.

Data on these indirect outcomes are likely to be used to estimate QALYs as final health outcomes.

Study design

We will prioritise RCTs for inclusion in the systematic review of clinical effectiveness. Where RCTs of technologies are not identified we will consider non-RCTs and controlled observational studies for inclusion, providing they include relevant outcomes.

Systematic reviews will be retrieved only to check their reference lists for potentially relevant studies. However, to ensure the workload is manageable within available time and resources we may include the aforementioned Cochrane systematic review of BIS which included 31 RCTs (Punjasawadwong and colleagues[34]). The Cochrane review had similar inclusion criteria to the current review and was last updated in May 2009. Rather than search for and review all studies of BIS, it is proposed that we summarise the findings of the Cochrane review and supplement it by reviewing any relevant studies published since May 2009.

Search strategy

A comprehensive search strategy will be devised, tested and applied to a number of electronic databases by an experienced Information Scientist (see *Appendix 1* for the MEDLINE strategy). Electronic databases to be searched include: MEDLINE (Ovid); MEDLINE In-Process & Other Non-Indexed Citations (Ovid); EMBASE (Ovid); The Cochrane Library (CDSR; CENTRAL); DARE; HTA; NHS Economic Evaluation Database (NHS EED); and EconLit.

Databases will be searched from 1995 to the present day (for BIS the search will be from May 2009 to the present day, supplementing the Cochrane systematic review). In addition, contact will be made with experts in the field to identify any relevant studies. Reference lists of included studies will be checked for any potentially relevant studies. Research in progress will be identified from the following databases: Current Controlled Trials; ClinicalTrials.gov; NIHR-Clinical Research Network Portfolio; WHO ICTRP (International Clinical Trials Registry Platform).

Studies published in the last two years as abstracts or conference proceedings will be included only if sufficient details are presented to allow appraisal of the methodology and the assessment of results to be undertaken.

Only articles published in the English language will be included.

For the cost-effectiveness assessment, searches for other evidence to inform cost-effectiveness modelling will be conducted as required and may include a wider range of study types.

The titles and abstracts of studies identified by the search strategy will be assessed for potential eligibility using the inclusion/exclusion criteria detailed above. Full papers of studies that appear potentially relevant will be requested for further assessment. These will be screened by one reviewer and checked by a second, and a final decision regarding inclusion will be agreed. Any disagreements will be resolved by discussion, with involvement of a third reviewer where necessary.

Data extraction strategy

All included studies will undergo data extraction using a structured piloted template. Each study will be extracted by one reviewer and checked by a second for accuracy. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

Quality assessment strategy

The methodological quality of all included studies will be appraised by one reviewer, and checked by a second. Any disagreements between reviewers will be resolved by consensus or if necessary by arbitration by a third reviewer.

RCTs will be appraised using the Cochrane Collaboration Risk of Bias criteria. Any non-randomised and observational studies included will be appraised using criteria developed by Spitzer and colleagues (1990).

Methods of analysis/synthesis

Studies will be synthesised through a narrative review with tabulation of results of included studies. Quantitative synthesis of results will be contingent on the data available. Meta-analysis using Cochrane Review Manager (REVMAN) software will be considered where appropriate (e.g. if there are several high quality studies of the same design) and sources of heterogeneity will be investigated.

Report methods for synthesising evidence of cost-effectiveness

Review of published cost-effectiveness studies

The methods detailed above will be used to systematically review the cost-effectiveness literature. The inclusion and exclusion criteria are similar to that of the systematic review of clinical effectiveness, with the exception of study design and outcomes. Studies will be included if they are full economic evaluations, assessing both costs and consequences, of the specified technologies (e.g. reporting cost per patient, cost per episode of intraoperative awareness or cost per QALY). The quality of the included economic evaluations will be assessed using a critical appraisal checklist based upon that proposed by Drummond and colleagues (2005) and Philips and colleagues (2006). The data from these studies will be tabulated and discussed in a narrative review.

Where presented, HRQoL data will be extracted from studies included in both the systematic review of clinical effectiveness and the systematic review of cost-effectiveness. In addition, a targeted literature search will be conducted specifically for publications reporting HRQoL or health state utility for adults with episodes of intraoperative awareness. Where available, QoL data will be used in our economic model.

Evaluation of costs and cost-effectiveness

A comparison of the costs and consequences of depth of anaesthesia monitoring will be made using decision-analytic models. The structure of the models will be informed by the systematic review of cost-effectiveness and other systematic searches of the literature and, where necessary, using guidelines and expert opinion. The model will be constructed according to standard modelling guidelines (Phillips and colleagues (2006) and a full explanation of our methods for formulating model structure and deriving parameter values will be given in the assessment report. The perspective will be that of the NHS and Personal Social Services (PSS). The outcome will be reported as cost per patient, cost per intraoperative awareness avoided and cost per quality-adjusted life-year (QALY) gained, where possible.

The decision tree model will include the costs of the anaesthesia-monitoring device (including the module, the sensors, and, if applicable, the monitors), and any savings associated with reduced use of anaesthesia, fewer side effects and improved recovery time from the anaesthesia. We will aim to assess the HRQoL impact of episodes of intraoperative awareness. If good HRQoL data are available the model will include health benefits in terms of QALYs. In the case where insufficient published HRQoL data are available it will be necessary to elicit HRQoL values from clinical experts or to conduct threshold analyses using a range of estimates. The time horizon will be a patient's lifetime (or shorter if appropriate) in order to reflect long-term health gains. Both costs and benefits will be discounted at 3.5%.

Parameter values will be obtained from the relevant research literature, including our own systematic review of clinical and cost-effectiveness. Sources for parameters will be stated clearly. Resource use will be specified and valued from the perspective of the NHS and PSS. Costs will be derived from primary data from previous studies, and national and local NHS unit costs. If insufficient data are retrieved from published sources, costs may be obtained from individual NHS Trusts or groups of Trusts.

Uncertainty will be explored through both one-way sensitivity analyses and scenario analyses. A probabilistic sensitivity analysis probabilistic sensitivity analysis will be undertaken if both the data and modelling approach permit this. The outputs of any probabilistic sensitivity analysis will be presented using plots of the cost-effectiveness plane and cost-effectiveness acceptability curves.

The model will be validated by checking the model structure, calculations and data inputs for technical correctness. The structure will be reviewed by clinical experts for appropriateness for the clinical and diagnostic pathways. The robustness of the model to changes in input values will be tested using sensitivity analyses.

References

Drummond M, Sculpher M, Torrance G, O'Brien B, Stoddart G. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press; 2005.

Philips Z, Bojke L, Sculpher M, *et al*. Good practice guidelines for decision-analytic modelling in health technology assessment: A review and consolidation of quality assessment. *Pharmacoeconomics* 2006; **244**, 355–71.

Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. *Cochrane Database Syst Rev* 2007; **4**: CD003843.

Spitzer W, Lawrence V, Dales R, Hill G, Archer M, Clarck P, *et al*. Links between passive smoking and disease: a best evidence synthesis. *Clin Invest Med* 1990; **13**, 17–42.