Confidential

Evidence Assessment and Analysis Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Clinical Excellence

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1. Title of the project

Depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend)

2. Name of External Assessment Group (EAG) and project lead

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3. Plain English Summary

Patients undergoing general anaesthesia for operations usually have their vital signs and other markers checked throughout the operation to ensure that, amongst other things, they are sufficiently unconscious. If too much anaesthesia has been used the health of the patient may be at risk and it may take them longer to recover from the operation. However, if not enough anaesthesia has been used patients may be more likely to be aware of their surroundings during the operation, and this may have short and long-term effects, including depression and anxiety. Observation of vital signs and markers may not always accurately indicate unconsciousness and consequently devices have been developed to measure and interpret patient electrical brain activity (e.g. 'E-entropy', 'Bispectral Index'). Most of these use a module which measures brain activity via sensors placed on the patient's forehead. The

module is linked to a monitor which visually displays the output (e.g. a numerical scale) which the anaesthetist then uses to judge depth of unconsciousness, and adjust the dose of anaesthetic if necessary. There is a need to assess how effective these devices are in determining unconsciousness, and to examine their cost effectiveness.

This project will do a literature search of a number of medical databases and will review relevant studies of the devices. The results of the studies will be summarised in terms of the ability of the devices to detect patient awareness during the operation, and other factors. The costs of the devices will be identified and an economic model will be constructed to estimate the benefits to the patient of the devices in relation to how much they cost. Where possible the patient's quality of life will be taken into account in judging how cost-effective the devices are. The results of the project will be used by the National Institute for Health and Clinical Excellence (NICE) to make guidance to the National Health Service in England and Wales on the use of the devices.

4. Decision problem

4.1 Purpose of the decision to be made

The purpose of anaesthesia monitoring is to ensure adequate sedation of the patient under general anaesthesia. If anaesthesia is too deep the patient may be at risk of adverse effects, such as a prolonged recovery time. However, if anaesthesia is not deep enough patients may be more likely to experience awareness of their surroundings, and this may have short-term and long-term psychological effects, including depression and anxiety. Optimum anaesthetic dosing may also potentially lead to drug cost savings.

Currently anaesthetists generally use clinical observation of vital signs and other markers to assess unconsciousness and the possibility of awareness. However, clinical observation alone may not be a reliable surrogate marker of anaesthetic depth.[1] As an alternative, technologies have been developed using electroencephalography (EEG) to measure and interpret patient electrical brain activity to provide a measure of unconsciousness.

The aim of this project is to assess the clinical-effectiveness and cost-effectiveness of technologies to monitor the depth of anaesthesia in surgical patients undergoing general anaesthesia.

4.2 Clear definition of the intervention

A number of EEG based technologies are available. Most comprise a module which measures electrical brain activity via sensors placed on the patient's forehead. The module is linked to a monitor which displays the processed monitoring output (e.g. a numerical scale) which the anaesthetist then uses to judge depth of unconsciousness. The following technologies are proposed for the scope of this assessment.

4.2.1 E-Entropy module (GE Healthcare)

Entropy monitoring in anaesthesia has been studied over the last ten years. E-Entropy (previously known as M-Entropy) is designed to aid the management of general anaesthesia in patients by measuring irregularity in spontaneous brain and facial muscular activity. It uses a proprietary algorithm to process EEG and frontal electromyography (FEMG) data to produce two values that indicate the depth of anaesthesia. The first value, response entropy (RE), is based on both EEG and FEMG signals and provides an indication of the patient's responses to external stimuli and signal early awakening. The second value, state entropy

(SE), is a stable parameter based on EEG and may be used to assess the hypnotic effect of anaesthetic agents on the brain.

Highly irregular signals where the wavelength and amplitude vary over time produce high values of entropy and indicate that the patient is awake. Regular signals with a constant wavelength and amplitude over time produce low or zero entropy values indicating a low probability of recall and suppression of brain electrical activity. The RE scale ranges from 0 (no brain activity) to 100 (fully awake) and the SE scale ranges from 0 (no brain activity) to 91 (fully awake). The clinically relevant target range for entropy values is 40-60. RE and SE values near 40 indicate a low probability of consciousness.

E-Entropy is a plug-in module that is compatible with the Ohmeda S/5 Anaesthesia monitor and S/5 Compact Anaesthesia monitor using software L-ANE03(A) and L-CANE03(A), and all subsequent software releases since 2003.

4.2.2. Bispectral Index (BIS) (Covidien)

The BIS system, introduced in 1994, uses a sensor on the patient's forehead to measure electrical activity in the brain before using proprietary algorithmic analysis to process the EEG data and calculate a number between 0 (absence of brain electrical activity) and 100 (wide awake). This provides a direct measure of the level of patient consciousness. The target range of BIS values during general anaesthesia is 40-60 which indicates a low probability of consciousness.

Other manufacturers (Mennen Medical, Philips, Dräger) have licensed the BIS (or BISx) technology from Covidien in order to produce BIS modules that are compatible with their anaesthesia systems.

4.2.3 Narcotrend (Narcotrend)

The Narcotrend monitor automatically analyses the raw EEG using spectral analysis to produce a number of parameters. Multivariate statistical methods using proprietary pattern recognition algorithms are then applied to these parameters to provide a visually classified EEG. The EEG visual classification scale is from stage A (awake) to stage F (very deep hypnosis) with stage E indicating the appropriate depth of anaesthesia for surgery. As a refinement to the A to F scale, an EEG index (100 = awake, 0 = very deep hypnosis) is also calculated.

4.3 Populations and relevant subgroups

Depth of anaesthesia monitoring can be used on patients undergoing general anaesthesia for surgery. Certain types of surgical procedures, including cardiac procedures, surgery for trauma, obstetric surgery, and airways surgery, necessitate lower anaesthetic dose and are therefore thought to increase the risk of intraoperative awareness. People with a high American Society of Anestheologists (ASA) physical status classification grade are may be at increased risk of awareness. Depth of anaesthesia monitoring can be used in children, though the E-entropy has not been validated for paediatric patients below two years of age. Children are thought to be at increased risk of intraoperative awareness. Elderly patients who receive high doses of anaesthetic are thought to be at increased risk of post-surgical cognitive dysfunction.[2]

Anaesthesia monitoring can be affected by factors such as heavy alcohol intake, chronic benzodiazepine or opioid use, or current protease inhibitor therapy.[3] Monitoring may also be affected in patients with neurological disorders (e.g. epilepsy, dementia, Parkinson's disease).

4.4 Place of the intervention in the treatment pathway(s)

In UK health care settings general anaesthesia is usually administered in an anaesthetic room[4], following which the patient is transferred to the operating theatre. Monitoring of clinical signs (see Section 4.5) can commence prior to administration of general anaesthesia, and continue until surgery is complete and the patient is moved from the theatre to the recovery room (or to intensive care or a high dependency unit). Supplementary monitoring devices such as EEG based technologies (as described in Section 4.2) may also be attached during anaesthesia induction, and continued until surgery is complete, anaesthesia has ceased and the patient has entered the recovery phase.

4.5 Relevant comparators

Observation of clinical signs is the mainstay of anaesthesia monitoring. Prior to induction of anaesthesia a variety of monitoring devices may be attached to the patient including: a pulse oximeter (to measure oxygen levels); a non-invasive blood pressure monitor; an electrocardiograph (to measure heart rhythm); and a capnograph (to measure inhaled and exhaled carbon dioxide concentration). Devices are also used to measure airway pressure, minimum alveolar concentration (MAC) (to measure the potency of inhaled general anaesthetics) and the patient's temperature. For patients who receive muscle relaxants nerve stimulation may also be used to assess awareness. Other markers of awareness that are monitored include movement, lacrimation (tear production), and sweating. Of the range of clinical signs the key aspects observed are end-tidal anaesthetic gas concentrations (where inhaled anaesthetics have been used), pulse measurement, and electrocardiography.[5]

4.6 Key factors to be addressed (e.g. clinical and cost outcomes, further considerations, problematic factors)

A key issue in the assessment of anaesthetic monitoring will be the reliable and valid measurement of intraoperative awareness. Assessment of awareness may take place during anaesthesia using methods such as the isolated forearm technique (to assess the patient's physical response to verbal commands), or post-operatively using patient questionnaires. The term 'wakefulness' describes the ability of a patient to respond to a command during general anaesthesia without recollection of this in the post-operative period. Implicit awareness exists without conscious recall but may or may not influence patient's health afterwards. However, it is problematic to identify episodes of intraoperative awareness that the patient cannot recall experiencing, and to assess what impact this may have had on them. Post-operative word stem tests are sometimes used to detect both explicit and implicit memory of words that had been presented to the patient through headphones during their surgery.

In terms of post-operative assessment, the proportion of patients reporting possible awareness may vary according to the measurement instrument used. The Brice Interview[6] has been commonly used in clinical research to assess awareness since the early 1970s, and over time there have been a number of variants of this instrument. Some instruments may be more sensitive than others in assessing awareness, resulting in variations in estimates. Some clinical trials have sought to enhance reliability and validity by administering questionnaires at multiple time points following surgery, and reported occurrences of awareness verified by an independent committee.[3]

Some monitoring technologies may be considered as 'stand alone' due to their compatibility with existing monitoring display equipment in the operating theatre. Other technologies (e.g. E-Entropy) appear to only be compatible with monitors from the same manufacturer. Cost analysis may therefore need to take into account the monitor as well as the module.

4.7 Areas of agreement at the scoping workshop that are outside the scope of the appraisal and therefore do not require any detailed assessment (*e.g. key factors for which evidence is already accepted*).

The following technologies were excluded from the scope of this appraisal during the scoping phase: AePEX, SEDline, NeuroSENSE, and the Cerebral State Monitor. Non-EEG based monitoring methods, specifically: SmartPilot View, Med-Storm stress detector, oesophageal motility, forehead galvanometry and the isolated forearm technique were also excluded from the scope.

4.8 Existing research

Scoping searches have identified a number of studies evaluating depth of anaesthesia monitors, some of which have used Randomised Controlled Trial (RCT) designs, and which have included clinical outcomes (e.g. intraoperative awareness[3;7]; reductions in anaesthetic use[8-10]; recovery/emergence times[3;7]; psychological sequelae from intraoperative awareness[3]). A Cochrane systematic review included 31 RCTs of BIS monitoring compared to standard clinical observation and assessed a range of clinical outcomes.[11]

Initial scoping searches have also identified some relevant cost effectiveness studies.[8;12;13] These studies have considered the cost effectiveness of BIS monitoring in terms of changes in the use of anaesthetic agents, anaesthetic side effects and time to wake-up and discharge from the post-anaesthesia care unit (PACU). The studies have estimated the cost savings from these monitoring approaches, together with the direct costs of the BIS monitoring device and electrodes. The cost of BIS per patient varied according to the assumptions used for the cost of the device. One study also assessed the cost effectiveness of other devices in addition to BIS.[13] None of the studies have estimated the health benefits obtained from reduced episodes of intraoperative awareness.

5. 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 Centre for Reviews & Dissemination (CRD) guidance for undertaking reviews in health care.[14]

5.1 Population

The relevant study population for this assessment is patients receiving general anaesthesia for surgery, including adults and children in whom the technology is licensed. Elderly and obese patients undergoing general anaesthesia 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.

5.2 Interventions

- E-Entropy
- Bispectral Index (BIS)
- Narcotrend

5.3 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.

5.4 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, anti-sickness drugs and muscle relaxants.
- Health related quality of life (HRQoL)

Data on these indirect outcomes are likely to be used to estimate Quality-Adjusted Life Years (QALYs) as final health outcomes.

5.5 Study design

We will prioritise RCTs for inclusion in the systematic review of clinical effectiveness (see Section 4.8). Where RCTs of technologies are not identified we will consider non-randomised controlled trials and controlled observational studies for inclusion, providing they include relevant outcomes as specified in Section 5.4.

Systematic reviews will only be retrieved in order 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.[15] 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.

5.6 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 (Ovid)*;* Embase (Ovid); the Cochrane Library (Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials), the Database of Abstracts of Reviews of Effectiveness (DARE); Health Technology Assessment Database (HTA); NHS Economic Evaluation Database (NHS EED); 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[15] – see Section 5.5). 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; Clinical Trials.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 (see Section 6) 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 which 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.

5.7 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.

5.8 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[16;17]. Any non-randomised and observational studies included will be appraised using criteria developed by Spitzer[18] (see Appendix 2).

5.9 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.

6. Report methods for synthesising evidence of cost effectiveness

6.1 Review of published cost-effectiveness studies

The methods detailed in section 5 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 as described in section 5.2, 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 et al.[19] and Philips et al.[20] 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 health related quality of life (HRQoL) or health state utility for adults with episodes of intraoperative awareness. Where available, quality of life data will be used in our economic model (see section 6.2).

6.2 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[20] 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 (PSA) will be undertaken if both the data and modelling approach permit this. The outputs of any PSA 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.

7. Handling information from the companies

Any 'commercial in confidence' data provided by a manufacturer and specified as such will be highlighted in blue and underlined in the assessment report (followed by an indication of

the relevant company name e.g. in brackets). Any academic-in-confidence data provided will be highlighted in yellow and underlined.

8. Competing interests of authors

None reported.

9. Timetable/milestones

Milestone	Date to be completed
Progress report to NETSCC, HTA	9th February 2012
Draft report submitted to NICE	5th March 2012
Submissionof final report to NETSCC, HTA; NICE	2nd April 2012

References

(1) Thomas G, Morgan M. Monitoring neuromuscular blockade and depth of anaesthesia. 12[6], 271-274. 1-6-2011.

(2) Hudson AE, Hemmings HC. Are anaesthetics toxic to the brain? *British Journal of Anaesthesia* 2011.

(3) Myles PS, Leslie K, McNeil J, Forbes A, Chan MT. Bispectral index monitoring to prevent awareness during anaesthesia: the B-Aware randomised controlled trial. *Lancet* 2004; 363(9423):1757-1763.

(4) Bromhead HJ, Jones NA. The use of anaesthetic rooms for induction of anaesthesia: a postal survey of current practice and attitudes in Great Britain and Northern Ireland. *Anaesthesia* 2002; 57(9):850-854.

(5) The Association of Anaesthetists of Great Britain and Ireland. Recommendations for Standards of Monitoring During Anaesthesia and Recovery. 4th Edition. 2007. London, The Association of Anaesthetists of Great Britain and Ireland.

(6) Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. *Br J Anaesth* 1970; 42(6):535-542.

(7) Gruenewald M, Zhou J, Schloemerkemper N, Meybohm P, Weiler N, Tonner PH et al. M-Entropy guidance vs standard practice during propofol-remifentanil anaesthesia: a randomised controlled trial. *Anaesthesia* 2007; 62(12):1224-1229.

(8) Liu SS. Effects of Bispectral Index monitoring on ambulatory anesthesia: a meta-analysis of randomized controlled trials and a cost analysis. *Anesthesiology* 2004; 101(2):311-315.

(9) Aime I, Verroust N, Masson-Lefoll C, Taylor G, Laloe PA, Liu N et al. Does monitoring bispectral index or spectral entropy reduce sevoflurane use? *Anesth Analg* 2006; 103(6):1469-1477.

(10) Vakkuri A, Yli-Hankala A, Sandin R, Mustola S, Hoymork S, Nyblom S et al. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. *Anesthesiology* 2005; 103(2):274-279.

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

(12) Abenstein JP. Is BIS monitoring cost-effective? *Conf Proc IEEE Eng Med Biol Soc* 2009; 2009:7041-7044.

(13) Nielsen JS, Thogersen B, Ording H. Monitoring depth of anaesthesia - a health technology assessment. 2007. Copenhagen, Danish Centre for Health Technology Assessment.

(14) Centre for Reviews and Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. Third edition. 2009. York Publishing Services Ltd., CRD.

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

(16) Higgins JPT, Altman DG, G+©tzsche PC, J++ni P, Moher D, Oxman AD et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343.

(17) Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011. The Cochrane Collaboration.

(18) 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 13, 17-42. 1990.

(19) Drummond MF, O'Brien B, Stoddart GL, Torrance GW. Methods for the economic evaluation of health care programmes (3rd edition). Oxford University Press; 2005.

(20) Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technology Assessment* 2004; 8(36).

10. Appendices

Appendix 1 –Medline (Ovid) search strategy

1. ("E-Entropy" or "M-Entropy" or Narcotrend).mp.
2. (entropy adj5 (module* or technolog* or system* or monitor* or machine*)).tw.
3. (entropy adj2 (state or response or spectral)).tw.
4. 2 or 3
5. 1 or 4
6. monitoring intraoperative/
7. consciousness monitors/
8. ("automated responsiveness" and (monitor* or measur* or machine*)).tw.
9. sedation monitor*.tw.
10. sedation measurement*.tw.
11. exp Anesthesia, General/
12. exp Anesthetics, General/
13. (an?esthetic* or an?esthesia or an?esthetist*).tw.
14. Intraoperative Period/
15. Anesthesia, Intravenous/
16. Anesthetics, Inhalation/
17. Anesthesiology/
18. exp Infusions, Intravenous/
19. Surgical Procedures, Operative/
20. General Surgery/
21. (surgery or surgical).tw.
22. Perioperative Period/
23. Signal Processing, Computer-Assisted/
24. Intraoperative Complications/
25. Perioperative Care/
26. Monitoring, Physiologic/
27. Adjuvants, Anesthesia/
28. Electromyography/
29. exp Electroencephalography/
30. Mental Recall/
31. Wakefulness/
32. Consciousness/
33. Perception/
34. Intraoperative Awareness/ or Awareness/
35. Arousal/
36. Deep Sedation/
37. Conscious Sedation/
38. Drug Therapy, Computer-Assisted/
39. Pain Measurement/
40. cerebral cortex/de
41. Evoked Potentials/ or Evoked Potentials Auditory/
42. Signal Processing, Computer-Assisted/
43. (surgery or surgical or operating or operation*1).tw.
44. (intraoperative* or "intra-operative*" or "intra operative*").tw.
45. (perioperative* or "peri-operative*" or "peri operative*").tw.
46. "depth of anaesthesia monitor*".tw.
47. "depth of anesthesia monitor*".tw.
48. "Anesthesia and Analgesia"/
49. Postoperative Period/
50. (postoperative or post?operative).tw.

51. (recall* or aware* or memory or memories or wake* or awake* or arous* or cry* or sweat* or tear*1 or dream* or remember* or movement* or grimac*).tw.
52. (EEG or EMG or FEMG or encephalogra* or electroencephalogra* or electromyogra*).tw.
53. Brice.tw.
54. or/6-53
55. 5 and 54
56. limit 55 to (english language and yr="1995 -Current")
57. animals/
58. 56 not 57
59. (letter or comment or editorial).pt.
60. 58 not 59
61. crystal*.tw.
62. 60 not 61
63. coma/ or coma.tw.
64. 62 not 63
65. (("bispectral Index" or "bi-spectral index" or "bi spectral index") adj5 (module* or technolog* or system* or monitor* or machine*)).mp.
66. ((BIS or BISx) adj5 (module* or technolog* or system* or monitor* or machine*)).mp.
67. (anesth* adj20 (BIS or BISx)).tw.
68. (anaesth* adj20 (BIS or BISx)).tw.
69. or/65-68
70. "behavio?ral inhibition system".tw.
71. 69 not 70
72. ((surg* adj20 "BIS") or "BISx").tw.
73. 71 or 72
74. 54 and 73
75. limit 74 to (english language and humans and yr="2009 - 2011")
76. 75 not 59
77. 76 not 64
78. Anesthesia, Local/
79. (local adj1 an?esth*).tw.
80. 78 or 79
81. 77 not 80

Appendix 2 – Quality assessment criteria for clinical-effectiveness studies

Cochrane Risk of Bias criteria for RCTs [16;17]

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation.	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence.
Allocation concealment.	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting.	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Quality assessment criteria for observational studies

These quality criteria were adapted from Spitzer and colleagues.[18] The original checklist was modified to include items of particular relevance to assessing observational studies.

1. Does the trial use proper random assignment?
   A study with proper random assignment would include multiple conditions with random assignment and would use an appropriate method for the assignment (e.g., random numbers table, computer generated, etc.) with allocation concealment.
2. Did the study use proper sampling?
   A study with proper sampling would allow for all patients to be equally likely to enter the study (e.g., patients selected consecutively or randomly sampled).
3. Was the sample size adequate?
   Proper sample size enables adequately precise estimates of priority variables found to be significant (e.g., can compute CI within relatively small range or relatively small SEM).
4. Were the criteria for definition or measurement of outcomes objective or verifiable?
   Good outcome measures would be defined by clear methods for measuring outcomes (i.e., an operational definition) that are public, verifiable and repeatable.
5. Were outcomes measured with blind assessment?
   In studies with blind assessment those evaluating outcomes are unaware of the treatment status of those being evaluated.
6. Were objective criteria used for the eligibility of subjects?
   Good eligibility criteria would use clear, public, verifiable characteristics that are applied for inclusion and exclusion.
7. Were attrition rates (%) provided?
   A study should report the number of patients who could not be contacted for outcome measures or later, e.g., drop-outs or withdrawals due to treatment toxicity.
8. Were groups under comparison comparable?
   Comparable groups show similar results across a reasonable range of baseline characteristics that could be expected to affect results.
9. Are the results generalisable?
   Generalisable results come from a sample population that is representative of the population to which results would be applied.