

Diagnostics Assessment Programme

Depth of anaesthesia monitors (E-Entropy, BIS and Narcotrend)

Final scope

November 2011

1 Introduction

The NICE Medical Technologies Advisory Committee identified the E-Entropy device (GE Healthcare), a depth of anaesthesia monitor, as potentially suitable for evaluation by the Diagnostics Assessment Programme based on a briefing note. The scope has been expanded to include alternative depth of anaesthesia monitors for monitoring the effects of general anaesthesia in patients undergoing operations, based on advice from experts and from the attendees at the scoping workshop held on 20th September 2011 and the assessment sub-group meeting held on 19th October 2011. This final scope describes the nature of the clinical evaluation and cost-effectiveness analysis to be undertaken. A glossary of terms, a list of abbreviations and a list of references are provided in appendices A, B and D respectively.

2 Description of the technologies

This section describes the properties of the depth of anaesthesia monitoring technologies based on information provided to NICE by the manufacturers and on information available in the public domain. NICE has not carried out an independent evaluation of these descriptions.

2.1 Purpose of the medical technologies

The depth of anaesthesia monitors are designed to monitor the effects of certain anaesthetic agents and the state of the central nervous system in patients undergoing general anaesthesia. The ability to monitor the levels of patient consciousness while undergoing general anaesthesia is clinically important because an inadequate level of anaesthesia can result in patient intra-operative awareness which can cause significant suffering followed by post-traumatic stress disorder in some patients. Conversely, an overdose of anaesthesia can result in a prolonged recovery and an increased risk of postoperative complications including permanent cognitive dysfunction for

some patients. The use of depth of anaesthesia monitors is claimed to provide a more accurate assessment of the level of anaesthesia and aid the tailoring of the anaesthetic dose to the individual patient. Tailored dosing potentially reduces drug consumption and the number of adverse effects, with possibly faster emergence from anaesthesia with an earlier patient discharge from the recovery room.

2.2 Product properties

2.2.1 Entropy module

The Entropy Module, E-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 electroencephalography (EEG) and frontal electromyography (FEMG) data to produce two values that indicate the depth of anaesthesia. The first value, response entropy (RE), is a fast-reacting parameter based on both EEG and FEMG signals, and is sensitive to facial muscle activation (2 second reaction time). It may provide 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.

The Entropy module is also capable of displaying the Burst Suppression Ratio (BSR). This indicates the ratio of the suppressed activity period to the total activity period (bursts and suppressed activity) in EEG in one minute. The target value for BSR during general anaesthesia is 0%. A higher BSR is typically seen with entropy values below 40 and can indicate unnecessarily deep anaesthesia.

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. Brain and facial muscular activity is recorded via a disposable sensor with three electrodes that are attached to the patient's forehead and a sensor cable that connects the sensor to the Entropy module. The module can produce continuous data which can be both stored and printed off and therefore is compatible with electronic record keeping.

2.2.2 Bispectral Index technology (BIS) (Covidien)

The BIS system 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 awareness with recall.

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.

2.2.3 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.

3 Target conditions / indications

3.1 General anaesthesia background

General anaesthesia is a reversible state of controlled unconsciousness resulting from the administration of medications to prevent awareness, recall, distress and movement in patients during surgery. It is estimated that 2.4 million people had a procedure that required the use of general anaesthetic in 2007. Approximately half of people who receive general anaesthesia will also receive muscle relaxants.

Individual variation in response to anaesthetic agents can lead to occasional over- or under-dose of anaesthesia in people. Some common side effects of general anaesthesia include vomiting, headaches and dizziness. Less common side effects include short- and long-term cognitive dysfunction, patient awareness and recall owing to inadequate levels of anaesthesia during surgery. Most studies suggest that between 1 and 2 people in 1000 experience awareness or a recall event during general anaesthesia, with a third of these patients experiencing pain¹. For those people who do experience awareness during anaesthesia there can be long term effects including anxiety, nightmares, flashbacks, clinical depression and in some cases post-traumatic stress disorder.

Awareness during anaesthesia is more likely during certain types of surgery in which lower levels of anaesthetic may be used such as cardiac surgery, airway surgery, obstetric surgery or emergency surgery for major trauma. The use of muscle relaxants can also increase the risk of patient perioperative awareness because they allow a lower level of anaesthetic to be used (this is aimed at reducing dangerous side effects). They also prevent patient movement which limits communication from the patient and so the anaesthetist has to use other clinical information to judge the patient's state of consciousness².

The accepted method for detecting awareness in patients following general anaesthesia is the structured modified Brice interview^{3,4} comprising 5 questions:

1. What was the last thing you remembered before you went to sleep?
2. What was the first thing you remembered after your operation?
3. Can you remember anything in between?
4. Can you remember if you had any dreams during your operation?
5. What was the worst thing about your operation?

The interview is usually conducted after the patient has recovered from general anaesthesia and then subsequently at 24 hours and 30 days postoperatively⁵. There are variations in the timing of interviews in different studies which may lead to differential detection of awareness. Multiple variants of this interview exist and are in use.

Other side-effects and risk associated with an overdose of general anaesthesia include a prolonged recovery and in severe cases, cardiovascular collapse and respiratory depression which can be fatal without cardiovascular and respiratory support. Another side-effect is postoperative cognitive dysfunction (POCD) in which a decline in cognitive function is seen after general anaesthesia⁶; this is most common in older people.

3.2 Care pathway

Before surgery under general anaesthesia, the anaesthetist reviews patient medical records and interviews the patient to determine the correct type and dose of anaesthetic agent and any monitoring that may be required for the individual patient. Some patients may receive a premedication before the administration of general anaesthetic. The purpose of this is to reduce the level of anaesthetic dose required and reduce side-effects such as nausea and vomiting. Monitoring devices (e.g. blood pressure, oxygen levels) are connected to the patient often in an anaesthetic room before the induction of general anaesthesia and removed after the patient has fully recovered from the effects of the anaesthesia. Monitoring devices may be temporarily disconnected when the patient is moved in or out of the operating theatre.

Induction of anaesthesia usually takes place in an anaesthetic room. General anaesthetic is administered intravenously or through the inhalation of anaesthetic gases. During induction the patient loses consciousness and progresses to analgesia and amnesia before moving to the operating theatre.

During surgery, other medications may be administered with general anaesthesia such as pain-relieving drugs, regional anaesthesia, antibiotics, anti-sickness drugs and muscle relaxants. In current NHS clinical practice, the patient response to anaesthesia during surgery is assessed by clinical observations such as crying and sweating, and the use of supplementary monitoring devices. These devices include an electrocardiograph (ECG) to measure the speed or rhythm of the heart, a non-invasive blood pressure monitor, a pulse oximeter to detect the pulse and calculate the amount of oxygen in the blood, a method of patient temperature control, a device to monitor volatile agent concentration and provide a MAC value, a nerve stimulator (if a muscle relaxant is used) and a capnograph to monitor the inhaled and exhaled concentration of carbon dioxide. Additional monitoring equipment such as a cardiac output monitor may also be used for some people or certain types of surgery⁷.

After surgery, the administration of anaesthetic agents is ceased, reversal muscle relaxant drugs and pain relieving drugs are administered as appropriate and extubation occurs (if necessary) before the patient moves to the recovery room and regains consciousness. Once the patient has recovered from the anaesthetic and they meet the post-anaesthesia discharge criteria (based on the Aldrete scoring system), the patient can be discharged from recovery to a general ward. If the patient does not meet the discharge criteria they will remain in the recovery room until assessed by an anaesthetist. Following the medical assessment, a patient not achieving the discharge criteria will be transferred to an appropriate unit such as the High Dependency Unit (HDU).

4 Scope of the evaluation

4.1 Population

The main population group to be considered for this evaluation:

Individuals undergoing general anaesthesia

If there is sufficient evidence, specific groups of the population undergoing general anaesthesia such as older people and people with obesity may be considered separately if there is differential clinical effectiveness.

4.2 Interventions

The interventions for this evaluation are the depth of anaesthesia monitors: BIS, E-Entropy and Narcotrend.

4.3 Comparator

The combination of standard clinical observation (of crying and sweating) and anaesthesia monitoring including an ECG, a blood pressure monitor and a volatile agent concentration monitor (volatile anaesthesia only) will be the comparator to the depth of anaesthesia monitors in this evaluation. The isolated forearm technique is currently considered the gold standard for detecting awareness but as it is not standard practice in the NHS it will not be considered as the comparator for this evaluation.

4.4 Healthcare setting

The depth of anaesthesia monitors are intended for use during general anaesthesia and therefore, are expected to be used in secondary and tertiary care settings.

4.5 Health outcomes

Intermediate measures from depth of anaesthesia monitoring include:

- Probability of awareness
- Time to emergence from anaesthesia
- Aldrete safety score in the recovery room

Indirect clinical outcomes associated with the use of depth of anaesthesia monitoring may include:

- 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, anti-sickness drugs and muscle relaxants.
- Patient distress and sequelae resulting from perioperative awareness

Data on these indirect outcomes are likely to be used along with clinical utility scores to estimate Quality-Adjusted Life Years (QALYs).

5 *Modelling approach*

5.1 Existing models

A number of studies in the published literature have considered the cost-effectiveness of BIS monitoring in reducing the consumption of anaesthetic agents and the number of side effects, and increasing the speed of patient

recovery from anaesthesia^{8,9,10,11,12}. Resulting direct costs but no QALYs have been reported.

5.2 Modelling possibilities

A significant question that will need to be answered, through modelling if necessary, is 'how are all the data from monitors (e.g. ECG, blood pressure, concentration of anaesthetic agents) used to make clinical decisions during general anaesthesia?' The levels of awareness and associated sequelae along with the side-effects and risks associated with overdoses of anaesthetic agents will need to be determined and modelled to identify resulting changes in final health outcomes.

The incidence of perioperative awareness is higher in certain groups such as children or people with a high American Society of Anesthesiologists (ASA) grade, and during certain types of surgery such as cardiac surgery, airway surgery, obstetric surgery or emergency surgery for major trauma. The use of muscle relaxants and total intravenous anaesthesia can also increase the risk of perioperative patient awareness. Sensitivity analyses will be performed to address any differences in clinical effectiveness owing to variation in either the probability of perioperative awareness or the probability of an overdose of anaesthesia in specific patient groups.

5.3 Cost considerations

The cost analysis will be based on the UK NHS setting and comprise both NHS and Personal Social Services (PSS) costs.

Costs to be considered include:

- Costs of equipment, sensors, and supplies
- Staff and training of staff (including time monitoring patients in recovery)
- Maintenance
- Consumption of anaesthetic agents
- Use of the recovery room
- Medical costs arising from on-going care following depth of anaesthesia monitoring
- Cost of anaesthesia workstation (if an anaesthesia monitor is only compatible with specific workstations).

The cost of the Entropy module is £5,352 per operating theatre. The consumable cost is £217 per box of 25 sensors (£8.68 per patient assuming one sensor is used per patient). If a contract is placed for the purchase of sensors the module is provided free of charge.

The costs of the BIS Vista monitoring system and the BIS Vista bilateral system are £4,350 and £5,025 respectively. The consumable cost is dependent on the type of sensor used. The BIS Quatro sensors cost £362.50 per box of 25 sensors, the BIS paediatric sensors cost £400 per box of 25 sensors and the BIS bilateral sensors cost £210 per box of 10 sensors.

Cost data are not available at scoping for other BIS monitors or for Narcotrend.

6 Equality issues

NICE is committed to promoting equality of opportunity and eliminating unlawful discrimination on the grounds of age, disability, gender reassignment, race, religion or belief, sex, and sexual orientation, and to complying fully with legal obligations on equality and human rights.

The Entropy module is not validated for paediatric patients below two years of age.

Postoperative cognitive dysfunction is most common in older people.

The clinical effectiveness of depth of anaesthesia monitors may be affected when monitoring patients with neurological disorders (e.g. epilepsy, dementia, Parkinson's disease), trauma or their sequelae, or people taking psychoactive medication. Epileptic seizure activity may also cause interference with readings.

The clinical effectiveness of depth of anaesthesia monitors may be affected when monitoring individuals who have levels of alcohol in their system or are taking high dose opiates, drugs that increase metabolism, high dose beta blockers, anti-retroviral drugs.

Appendix A Glossary of terms

Aldrete safety score

A scoring system that is used to determine when patients have recovered from anaesthesia and can be safely discharged to a general ward. The condition of the patient is scored in a number of categories such as respiration, consciousness and activity. The total score of all the categories determines the overall Aldrete safety score.

Algesimeter

A device used to measure sensitivity to pain.

Algorithm

A step-by-step procedure for mathematical calculations or decision making.

Amplitude

The maximum height of an EEG signal during one wave cycle.

Amnesia

Loss of memory.

Analgesia

Loss of sensitivity to pain.

ASA Grade

The American Society of Anaesthesiologists (ASA) physical status classification system which is used to assess the fitness of patients before surgery.

Burst Suppression Ratio (BSR)

Ratio of the suppressed activity period to the total activity period (bursts and suppressed activity) in EEG in one minute.

Burst count

Number of bursts in activity in EEG.

Capnograph

An instrument to monitor the inhaled and exhaled concentration and carbon dioxide.

Conductance

The ability of electrical signals to flow along a certain path.

Electrocardiograph (ECG)

An instrument to measure the speed or rhythm of the heart

Electroencephalography (EEG)

A recording of the brain's spontaneous electrical activity over a period of time.

Electromyography (EMG)

A technique for recording the electrical activity from skeletal muscles.

Extubation

The process of removing a breathing tube from the patient

Frontal electromyography (FEMG)

A technique for recording the electrical activity from the facial muscles.

General anaesthesia

A reversible state of controlled unconsciousness resulting from the administration of medications to prevent awareness, recall, discomfort and movement in patients during surgery.

Perioperative awareness

Patient awareness during the three phases of surgery: preoperative, intraoperative and postoperative.

Isolated forearm technique

A technique where, before the administration of muscle relaxants, a tourniquet is applied to the upper arm and inflated above systolic pressure to prevent the muscle relaxants from affecting the arm. Spontaneous movement of the arm or movement in response to a command indicates a degree of patient consciousness although this may not be explicit awareness. Once movement has ceased, the tourniquet is deflated.

Minimum alveolar concentration (MAC)

The minimum concentration of anaesthetic agent in the lungs at 1 atmosphere pressure that is required to prevent movement in 50% of individuals when exposed to a standard painful stimulus. It provides a measure of the potency of inhaled general anaesthetics.

Postoperative cognitive dysfunction (POCD)

Poor mental function such as confusion and forgetfulness following surgery.

Post-traumatic stress disorder (PTSD)

A severe anxiety disorder that can develop after a traumatic experience.

Quality-adjusted life year (QALY)

A measure of disease burden that includes the quality and length of life.

Pulse oximeter

An instrument to detect the pulse and calculate the amount of oxygen in the blood.

Response entropy (RE)

A fast-reacting parameter based on processed EEG and FEMG signals which is sensitive to facial muscle activation. It may provide an indication of the patient's responses to external stimuli and signal early awakening.

Sequelae

A pathological condition following from a disease, injury or trauma

State entropy (SE)

A stable parameter based on processed EEG signals which may be used to assess the hypnotic effect of anaesthetic agents on the brain.

Wavelength

The distance over which the wave cycle repeats.

Appendix B Abbreviations

ASA	American Society of Anestheologists
BSR	Burst Suppression Ratio
ECG	Electrocardiograph
EEG	Electroencephalography
EMG	Electromyography
FEMG	Frontal electromyography
MAC	Minimum alveolar concentration
PSS	Personal social services
POCD	Postoperative cognitive dysfunction
PTSD	Post-traumatic stress disorder
QALY	Quality-adjusted life year
RE	Response entropy
SE	State entropy

Appendix C Related NICE guidance

- CG13 Caesarian section (2004)
- CG26 Post-traumatic stress disorder (2005)
- CG112 Sedation in children and young people (2010)

Appendix D References

1. The Royal College of Anaesthetists. Risks associated with your anaesthetic: [Section 8: Awareness during general anaesthesia](#). 2010
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8. Klopman M.A. and Sebel P.S. Cost-effectiveness of bispectral index monitoring. *Current Opinion in Anaesthesiology* 2011; **24**: 177-181
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10. Bonhomme V. and Hans P. Monitoring depth of anaesthesia: is it worth the effort? *European Journal of Anaesthesiology* 2004; **21**: 423-428
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12. Liu S.S. Effects of Bispectral Index monitoring on ambulatory anesthesia: a meta-analysis of randomized controlled trials and a cost analysis. *Anesthesiology* 2004; **101**: 311-315

Appendix E Attendees of the assessment sub-group meeting

The following people were in attendance at the assessment sub-group meeting held on 19th October 2011:

	Name of representative	Job Title	Organisation
External Assessment Group	Dr Jeremy Jones	Health Economist	Southampton Health Technology Assessment Centre (SHTAC)
	Dr Jonathan Shepherd	Principal Research Fellow	Southampton Health Technology Assessment Centre (SHTAC)
Standing member	Dr Simon Fleming	Consultant in Clinical Biochemistry and Metabolic Medicine	Department of Clinical Chemistry, Royal Cornwall Hospital
Specialist committee members	Dr Andrew Smith	Consultant Anaesthetist	Royal Lancaster Infirmary
	Professor Anthony Fisher	Head of Department, Consultant Clinical Scientist	Royal Liverpool University Hospital
	Dr David Smith	Consultant/Senior Lecturer in Cardiac Anaesthesia (A+B)	Southampton University Hospitals NHS Trust
	Dr John Andrzejowski	Consultant in Anaesthesia & Neurointensive Care	Royal Hallamshire Hospital, Sheffield
	Mr John Hitchman	Lay representative	
	Professor Michael Wang	Professor of Clinical Psychology/Honorary Consultant Clinical Psychologist	University of Leicester

NICE staff in attendance:

Name	Title
Professor Adrian Newland	Chair, Diagnostics Advisory Committee
Nick Crabb	Associate Director, Diagnostics Assessment Programme
Hanan Bell	Technical Adviser, Diagnostics Assessment Programme
Jackson Lynn	Project Manager, Diagnostics Assessment Programme
Sarah Baggaley	Technical Analyst, Diagnostics Assessment Programme