National Institute for Health and Clinical Excellence

DIAGNOSTICS ASSESSMENT PROGRAMME

Evidence overview

Depth of anaesthesia monitors

–Bispectral Index, E-Entropy and Narcotrend-Compact M

This overview summarises the key issues for the Diagnostics Advisory Committee's consideration. It includes a brief description of the topic, a description of the analytical structure and model, a discussion of the analytical difficulties, and a brief summary of the results. It is not a complete summary of the diagnostics assessment report, and it is assumed that the reader is familiar with that document. This overview contains sections from the original scope and the diagnostics assessment report, as well as referring to specific sections of these documents.

1 Background

1.1 Introduction

The depth of anaesthesia monitor, E-Entropy (GE Healthcare), was referred by the Medical Technologies Advisory Committee (MTAC) for recommendations on its use in the NHS. Two other monitors, Bispectral Index (BIS) (Covidien) and Narcotrend-Compact M (MT MonitorTechnik) were identified during the scoping phase and included in the assessment as alternative technologies.

The purpose of this assessment is to evaluate the clinical and cost effectiveness of using these three monitors to monitor the effects of general anaesthesia in patients undergoing operations. Provisional recommendations on the use of these technologies in the NHS will be formulated by the Diagnostics Advisory Committee at the Committee meeting on 2 May 2012.

1.2 The condition(s)

1.2.1 General anaesthesia

General anaesthesia is a reversible state of controlled unconsciousness achieved with drugs used to prevent awareness, recall, distress and movement in patients during surgery. It is estimated that 2.4 million people received general anaesthesia in 2007. Approximately half of those who have a general anaesthetic also receive muscle relaxants.

Individual variation in response to anaesthetics can lead to occasional over- or under-dosing. Some common side effects of general anaesthesia include vomiting, headaches and dizziness. Less common side effects include short- and long-term cognitive dysfunction and 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 recall during general anaesthesia, with a third of these also experiencing pain. For those who experience awareness during anaesthesia there can be long-term effects such as 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 are often used. These include cardiac surgery, airway surgery, obstetric surgery or emergency surgery for major trauma. The use of muscle relaxants can also increase the risk of patient awareness because they allow a lower level of anaesthetic to be used (with the aim of reducing dangerous side effects). Muscle relaxants also prevent patients from moving. This limits the patient's ability to communicate with the surgical team and means that the anaesthetist has to use other clinical information to judge the patient’s state of consciousness.

The accepted method for detecting awareness in patients following general anaesthesia in research studies is the structured modified Brice interview comprising the following five questions:

- What was the last thing you remembered before you went to sleep?

- What was the first thing you remembered after your operation?
- Can you remember anything in between?
- Can you remember if you had any dreams during your operation?
- What was the worst thing about your operation?

The Brice interview is usually conducted after the patient has recovered from general anaesthesia and then again at 24 hours and 30 days after surgery. There is variation in the timing of interviews among studies which may lead to variation in the detection of patient awareness. There are also multiple variants of the Brice interview in use.

Side effects of general anaesthetic overdose include prolonged recovery and, in severe cases, cardiovascular collapse and respiratory depression (which can be fatal without cardiovascular and respiratory support). Postoperative cognitive dysfunction is another side effect and is most common in older people.

1.3 Diagnostic and care pathways

Before general anaesthesia, the anaesthetist interviews the patient and reviews their medical records to determine the type and dose of anaesthetic and any monitoring that may be needed. Some patients may receive a premedication before the administration of general anaesthetic. This is to allay anxiety and reduce side effects such as nausea and vomiting. Monitoring devices (for example, to monitor blood pressure and blood oxygen levels) are connected to the patient before general anaesthesia is induced. Monitoring devices are removed after the patient has fully recovered from the effects of the anaesthesia and may be temporarily disconnected when the patient is moved in or out of the operating theatre.

In the UK, anaesthesia is usually induced in an anaesthetic room. General anaesthesia is administered intravenously or by inhalation until the patient loses consciousness. Further anaesthetic procedures (for example, intubation of the trachea, placement of further monitoring) may be carried out before moving the patient into the operating theatre.

During surgery, other drugs may be given with the general anaesthesia. These may include pain-relieving drugs, regional anaesthesia, antibiotics, anti-emetics drugs and muscle relaxants. In current NHS clinical practice, a patient's 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 and 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 measurement , a device to monitor volatile agent concentration and provide a MAC (minimum alveolar concentration) 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 be used for some patients or certain types of surgery.

After surgery, the administration of anaesthetic is stopped, muscle relaxant drugs are reversed (if used) and pain killers are given as appropriate. The patient is extubated (if necessary) before being moved to the post anaesthesia care unit and regaining consciousness. Once the patient has recovered from the anaesthetic and meets the criteria for discharge after anaesthesia, they can be discharged from recovery to a general ward. If the patient does not meet the discharge criteria they remain in the post anaesthesia care unit until assessed by an anaesthetist. After this assessment, any patient not meeting the discharge criteria is transferred to an appropriate unit such as the high dependency unit.

1.4 Population

The population considered in this assessment is patients undergoing general anaesthesia. A population sub-group of individuals classified at high risk of awareness during general anaesthesia has also been included in the assessment because there was sufficient available evidence.

The scope requested separate analysis when sufficient evidence was available for specific groups in which there might be evidence of differential

effectiveness (such as older people and people with obesity). There was insufficient evidence for subgroup analysis.

2 The technologies

Conventional monitoring approaches can result both in cases of complications from over anaesthesia and cases of awareness resulting from under anaesthesia, and therefore a variety of depth of anaesthesia monitors have been developed with the aim of more appropriately monitoring anaesthetic dose. This evaluation is focussed on three monitors that are based on algorithms using EEG (electroencephalography) data and are currently marketed in the UK.

2.1 Technologies under assessment

2.1.1 Bispectral Index (BIS) (Covidien)

The Bispectral Index (BIS) system uses a sensor on the patient's forehead to measure electrical activity in the brain before using a proprietary algorithm 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 patient's response to anaesthetic drugs. The target range of BIS values during general anaesthesia is 40–60; this range 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.

2.1.2 E-Entropy (GE Healthcare)

The E-Entropy monitor measures 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 indicate 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 with variation of wavelength and amplitude over time produce high values of entropy and may indicate that the patient is awake. More ordered signals with less variation in 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 E-Entropy monitor 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 1 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. It is not compatible with other systems. 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, and therefore is compatible with electronic record-keeping. The manufacturer estimates that 45% of all UK operating theatres would be compatible with the E-Entropy monitor; for the

remaining 55% investment in new monitoring equipment may be needed for compatibility with the Entropy module.

2.1.3 Narcotrend-Compact M (MT MonitorTechnik)

The Narcotrend-Compact M monitor automatically analyses the raw EEG data 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 an automatically classified EEG. The basis for the development of the automatic classification functions were visually classified EEGs. The EEG 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.

2.2 Comparators

The combination of standard clinical observation (of crying and sweating) and one or more clinical markers such as pulse measurement, blood pressure and end-tidal anaesthetic gas concentration (for inhaled anaesthesia) is the comparator for this assessment. The isolated forearm technique is currently considered the gold standard for detecting awareness, but was not included as the comparator in the scope because it is not standard practice in the NHS.

3 The evidence

3.1 Clinical effectiveness

The External Assessment Group conducted a systematic review of the evidence on the clinical effectiveness of the three depth of anaesthesia monitors. Supplementary evidence provided by the manufacturers of the technologies is also included in the diagnostics assessment report.

Details of the systematic review can be found starting on page 33 of the diagnostics assessment report. Studies were included if one or more of the following outcomes was reported:

- probability of awareness during surgery

- patient distress and other sequelae resulting from awareness during surgery
- recovery status
- time to emergence from anaesthesia
- time to extubation
- time to discharge from the post anaesthesia care unit
- consumption of anaesthetic agents
- morbidity and mortality including post-operative cognitive dysfunction.

3.1.1 Bispectral Index (BIS)

Eleven randomised controlled trials comparing the clinical effectiveness of the Bispectral Index monitor with standard clinical monitoring were included in the systematic review. Five of these trials were conducted in children (aged 2–18 years). Two of the trials were conducted in populations with known risk factors (for example, patients undergoing cardiac or airway surgery) for awareness during surgery. These studies supplement the Cochrane review on 'Bispectral Index for improving anaesthetic delivery and postoperative recovery', which included 31 randomised controlled trials of BIS compared with standard clinical practice. All of these trials included in the Cochrane review were conducted in adults.

The method of administering general anaesthesia varied across the 11 trials. Five trials used inhaled anaesthetic (predominantly sevoflurane) for both induction and maintenance of general anaesthesia. Three other trials used intravenous anaesthesia (propofol) for both induction and maintenance of general anaesthesia (total intravenous anaesthesia). The remaining three trials used both intravenous and inhaled anaesthesia. Two used propofol for the induction of anaesthesia and sevoflurane for the maintenance of anaesthesia. Muscle relaxants were used in seven of the trials.

A total of six trials reported awareness during surgery as an outcome and three of these trials reported this as the primary outcome. In these three trials, there were 29 cases of awareness during surgery with BIS monitoring and 30 cases with standard clinical monitoring. One trial monitoring anaesthesia in

patients classified as at high risk of awareness during surgery reported 19 definite or possible cases of awareness in the group with BIS monitoring (n = 2861) compared with 8 definite or possible cases in the group with standard clinical monitoring (n = 2852). This difference was not statistically significant. A second trial of patients at increased risk of awareness receiving total intravenous anaesthesia, reported 8 cases of confirmed or possible awareness in the group with BIS monitoring (n = 2919) compared with 21 cases in the group with standard clinical monitoring group (n = 2309). The lower incidence of confirmed awareness in the group with BIS monitoring was statistically significant. A third trial reported 2 cases of awareness during surgery in the group with BIS monitoring (n = 67) compared with 1 casein the group with standard clinical monitoring (n = 61). Statistical significance was not reported. This trial was the only one to also report implicit awareness as measured by a word recognition test. The trial reported that the probability of post-operatively selecting a word presented during anaesthesia was higher with BIS monitoring (mean 0.371 ± 0.132) than with standard clinical monitoring (mean 0.323 ± 0.132). In addition, the probability of post-operatively selecting a word not presented during anaesthesia was lower with BIS monitoring (mean 0.315 ± 0.117) than with standard clinical monitoring (mean 0.338 ± 0.119). However, the statistical significance of these results was not reported. The three trials that did not report awareness as the primary outcome had no cases of awareness during surgery. These three trials were not designed to detect awareness during surgery and it is likely that the sample sizes were insufficient to detect this rare outcome..

The Cochrane review on BIS included a meta-analysis of awareness during surgery with recall which included four trials in patients at high risk of awareness during surgery. This meta-analysis was updated by the EAG to include the two further studies in patients at high risk of awareness during surgery. After the addition of these two studies, the odds ratio increased from 0.33 to 0.45 indicating a statistically significant difference between groups, favouring BIS. However, there was a large amount of heterogeneity between the trials.

Six trials reported anaesthetic consumption as an outcome and two of these reported this as the primary outcome. Three of the trials showed a statistically significant reduction in the use of inhaled anaesthetic in the group with BIS monitoring compared with the group with standard clinical monitoring. The other three trials reported use of intravenous anaesthetic. Two of these trials reported a higher maintenance dose of anaesthetic with BIS monitoring compared with standard clinical monitoring, but there was no statistically significant difference between the two groups. The third trial reported a 25.3% reduction in the consumption of the intravenous anaesthetic propofol with BIS monitoring compared with standard clinical monitoring. No statistical significance was reported.

The Cochrane review on BIS included a meta-analysis of anaesthetic consumption, with separate analyses for inhaled anaesthetic consumption and intravenous anaesthetic consumption. When these meta-analyses were updated by the EAG the mean difference in inhaled anaesthetic consumption was slightly reduced from –0.16 to –0.15 but remained statistically significant. The mean difference in intravenous anaesthetic consumption was also slightly reduced from –1.44 to –1.33 but remained statistically significant.

Of the 11 trials, 5 reported time to extubation as a secondary outcome. All of these trials showed that time to extubation was reduced by 0.5–5 minutes with BIS monitoring compared with standard clinical monitoring. Two of these trials reported statistically significant results.

Five trials reported the time to discharge from the post-anaesthesia care unit as a secondary outcome and four of these trials were conducted in children. All of the trials showed that the time to discharge was shorter by 6.7–30 minutes in the group with BIS monitoring than in the group with standard clinical monitoring. These results were reported as statistically significant in all trials. However, the point at which the time to discharge began varies across the trials. One trial reported the time to discharge from the end of surgery and two others reported time to discharge from the end of general anaesthesia.

In the Cochrane review, 12 trials were included in the meta-analysis of the time to discharge from the post-anaesthesia care unit. The mean difference in the Cochrane review was –7.63 minutes in favour of BIS. The EAG did not update the Cochrane review for this outcome because of heterogeneity between studies.

3.1.2 E-Entropy

Seven randomised controlled trials comparing the clinical effectiveness of the E-Entropy monitor with standard clinical monitoring were included in the systematic review. Two of these studies were conducted in children (aged 3–12 years). None of the trials was conducted in populations with known risk factors for awareness during surgery.

The method of administering general anaesthesia varied across studies. Two trials used inhaled anaesthetic (sevoflurane) and three other trials used intravenous anaesthetic (propofol), for both induction and maintenance of general anaesthesia. Two trials used intravenous anaesthesia for induction followed by an inhaled anaesthetic for maintenance of general anaesthesia. All but one trial used muscle relaxants.

There was one case of awareness during surgery in the six trials that reported this outcome. This case occurred in the standard clinical monitoring group. All of the trials were small in sample size so rare events such as awareness during surgery may not have been detected.

Four trials showed a statistically significant reduction in the consumption of inhaled anaesthetic with E-entropy monitoring compared with standard clinical monitoring, although one of these trials showed no reduction in the total amount of anaesthetic consumed. In contrast, no statistically significant reduction in the consumption of intravenous anaesthesia was found in a trial reporting the consumption of intra-venous anaesthesia as a primary outcome. However, two trials that reported the consumption of intravenous anaesthesia as a secondary outcome did show statistically significant lower propofol consumption in the E-entropy monitoring compared with standard clinical monitoring.

Three trials reported time to extubation as a secondary outcome. All showed that time to extubation was shorter by approximately 3–4 minutes with E-entropy monitoring than standard clinical monitoring. Two of these trials reported statistical significance.

Two trials reported that the time to discharge from the operating room to the post-anaesthesia care unit was reduced by approximately 3–4 minutes with E-entropy monitoring compared with standard clinical monitoring. Both trials reported that this result was statistically significant. Only one trial reported the time to discharge from the post-anaesthesia care unit. The group with E-entropy monitoring was discharged sooner than the group with standard clinical monitoring, but the difference was not statistically significant.

3.1.3 Narcotrend-Compact M

Four randomised controlled trials comparing the clinical effectiveness of the Narcotrend-Compact M monitor with standard clinical monitoring were included in the systematic review. All of these were conducted in adults. None reported risk factors for awareness during surgery in the study populations.

The method of administering general anaesthesia varied across studies. Three trials used total intravenous anaesthesia (propofol-remifentanil or propofol-fentanyl) and one other trial used a mix of intravenous anaesthesia and inhaled anaesthetic (desflurane-remifentanil) for maintenance of general anaesthesia. Three trials used muscle relaxants.

There were no cases of awareness during surgery in the four trials reporting the clinical effectiveness of the Narcotrend monitor.

Of three trials that reported consumption of the anaesthetic, propofol, two showed a statistically significant reduction in the consumption with Narcotrend monitoring compared with standard clinical monitoring. The third trial showed no difference in propofol consumption between the two groups.

In one study that reported time to extubation as a primary outcome, no difference was shown between the group with Narcotrend monitoring and the group with standard clinical monitoring. Two studies that reported time to

extubation as a secondary outcome showed a statistically significant reduction of 1.6–6 minutes with Narcotrend monitoring compared with standard clinical monitoring.

Two trials reported a statistically significant reduction in the time to arrival at the post-anaesthesia care unit in the group with Narcotrend monitoring compared with the group with standard clinical monitoring.

3.2 Cost effectiveness

3.2.1 Bispectral Index (BIS)

One study was identified that met the inclusion criteria for the systematic review on the cost effectiveness of using a monitor to assess depth of anaesthesia compared with standard clinical monitoring.

The study used a simple calculation model to compare the cost-effectiveness of standard clinical monitoring alone with the addition of BIS monitoring to standard clinical monitoring. The cost per patient of BIS monitoring included the cost of the sensors and the monitor. An incidence of awareness during surgery of 0.04% was used for standard clinical monitoring with BIS monitoring and 0.18% was used for standard clinical monitoring alone. The study concluded that the addition of BIS monitoring was not cost effective. However, the study did not include health-related quality of life and there is uncertainty in the quality of the methodology.

3.2.2 E-Entropy and Narcotrend-Compact M

No studies were identified that included E-Entropy or Narcotrend monitoring and met the inclusion criteria for the systematic review on cost effectiveness.

4 Economic model

The EAG developed a decision-analytic model to assess the cost-effectiveness of using a monitor to assess the depth of anaesthesia plus standard clinical monitoring compared with standard clinical monitoring alone. The model evaluated costs from the perspective of the NHS and personal social services. Outcomes were expressed as quality-adjusted life years

(QALYs). Both costs and outcomes were discounted using a 3.5% annual discount rate. Separate economic analyses were conducted for each of the three technologies. No analyses were conducted to directly compare the technologies.

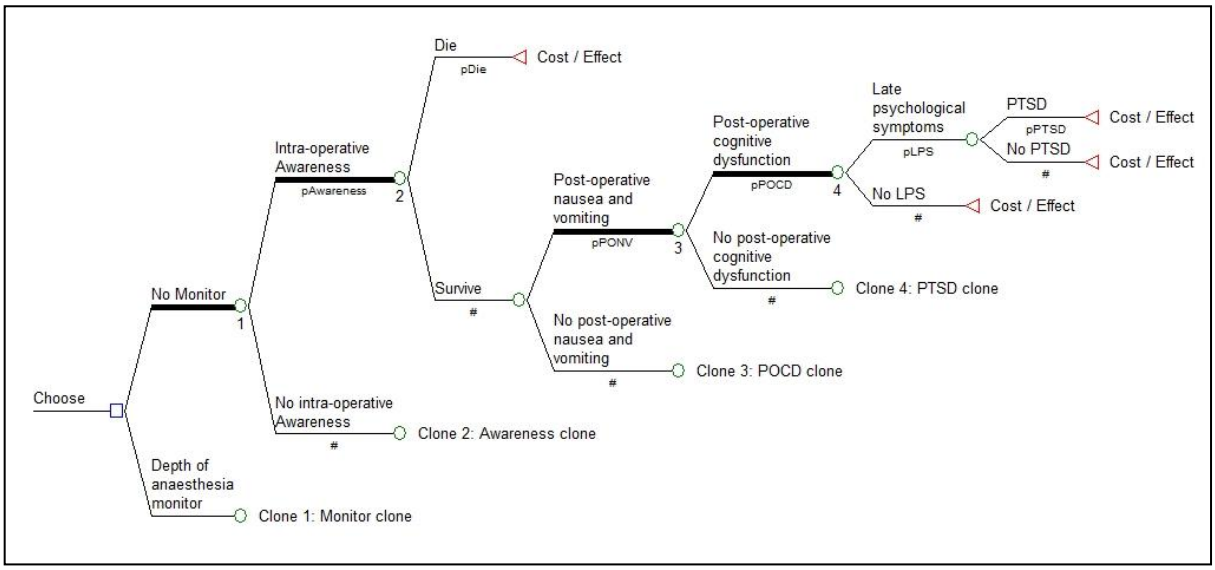
4.1 Model structure

A decision tree model was developed to model and compare the outcomes and costs resulting from the use of depth of anaesthesia monitors as opposed to standard clinical monitoring alone. The relevant clinical outcomes were those associated with over- and underdosing of general anaesthesia in the general surgical population and the population at high risk of awareness. Specifically, the risk of experiencing short-term complications (such as post-operative nausea and vomiting) and long-term complications (such as post-operative cognitive dysfunction), and the risk of experiencing awareness during surgery were included in the model.

The model was also used to estimate the costs of depth of anaesthesia monitoring and the costs of treating short- and long-term complications. It was assumed that the costs of monitoring clinical signs such as blood pressure and heart rate were common to depth of anaesthesia monitoring and standard clinical monitoring; therefore these were not included in the model. The main costs associated with standard clinical monitoring in the model were costs of anaesthesia, costs of complications related to anaesthesia and costs of managing long-term sequelae of awareness during surgery. No impact of short-term complications on quality of life was included in the model because they are expected to be of short duration.

Three separate models were developed, one for each monitoring system. However, the model structures were the same, with only the values for the parameters varying. The models used different values for the risks associated with usual care (without a depth of anaesthesia monitor) corresponding to the results in the respective trials. As a result, no direct comparisons of the monitors were performed. The structure of the model is shown in figure 1.

Figure 1 Structure of the decision tree model evaluating the cost effectiveness of depth of anaesthesia monitoring compared with standard clinical monitoring alone (page 96 of the diagnostics assessment report)



For each monitor, four analyses were performed, two each for the general surgical population and the population at high risk of awareness. For each of the two populations, two analyses were performed, one for total intravenous anaesthesia and one for mixed anaesthesia.

4.2 Model inputs

A summary of the model inputs can be found on pages 125–130 of the diagnostics assessment report.

4.2.1 Cost of depth of anaesthesia monitoring

Unit costs for depth of anaesthesia monitors included the acquisition cost of the monitor (annual cost assuming a 5-year effective life and converted to an average cost per patient based on assumptions of patient throughput) and recurring costs arising from the single-use sensors. The cost of the monitors varied from £4867 for the BIS monitor to £10,825 (the midpoint of a range of prices for Narcotrend). Sensor costs varied more widely, with costs per patient of £17.75, £8.68 and £0.56 for BIS, E-Entropy and Narcotrend respectively.

4.2.2 Cost of anaesthetic

Unit costs for propofol (£57) were taken from the British national formulary 62 and unit costs for inhaled anaesthetics (£76 for desflurane, £148 for sevoflurane) were obtained from University Hospital Southampton NHS Foundation Trust. The consumption of intravenous anaesthetics for total intravenous anaesthesia was based on data from two clinical trials (Gruenewald et al. (2007); Ellerkmann et al. (2010)) and the consumption of inhaled anaesthetic was estimated using an equation to calculate the cost per MAC unit time. The estimated anaesthetic consumption is shown on page 100 of the diagnostics assessment report.

4.2.3 Post-operative nausea and vomiting

The unit cost of treating post-operative nausea and vomiting was assumed to be the same for types of monitoring (£5.39 for ondansetron). A baseline risk of post-operative nausea and vomiting (30%) was based on data from the literature and used in the model for standard clinical monitoring and depth of anaesthesia monitoring.

4.2.4 Post-operative cognitive dysfunction

The baseline risk of post-operative cognitive dysfunction was based on data from the International Study of Post-Operative Cognitive Dysfunction. This study reported the incidence of post-operative cognitive dysfunction in patients over 60. The proportion of patients having surgery who are over 60 was estimated using data from HES online. The impact of depth of anaesthesia monitoring on post-operative cognitive dysfunction was estimated by applying odds ratios that were estimated from a study by Chan et al. (2010). The impact of post-operative cognitive dysfunction on quality of life was based on a study (Jonsson et al. 2006) evaluating the difference in mental state between people with and without cognitive dysfunction. The values used for post-operative cognitive dysfunction are shown on page 104 of the diagnostics assessment report.

4.2.5 Awareness during surgery

A baseline risk of 0.16% for awareness in the general population and a baseline risk of 0.45% for awareness in high-risk patients were pooled

estimates from studies identified by the EAG. The impact of depth of anaesthesia monitoring on awareness during surgery was derived from the meta-analysis of studies included in the systematic review of clinical effectiveness. Insufficient data were identified for the effectiveness of the Entropy and Narcotrend monitors so the odds ratios derived for the BIS monitor were used for all monitors. Different odds ratios were obtained from the meta-analysis depending on the type of anaesthesia. For high-risk patients receiving total intravenous anaesthesia the estimated odds ratio was 0.24 and for high-risk patients receiving mixed anaesthesia, the estimated odds ratio was 0.45. The same odds ratios were applied for patients not at high risk of awareness during surgery.

4.2.6 Late psychological symptoms and post-traumatic stress disorder

The probabilities of a patient experiencing late psychological symptoms such as anxiety and flashbacks, or post-traumatic stress disorder, were based on data from studies identified by the EAG (see table 1). The impact of post-traumatic stress disorder on quality of life was based on a number of studies and the cost of treating post-traumatic stress disorder was estimated from 'Post-traumatic stress disorder' (NICE clinical guideline 26).

Table 1 Rates per 10,000 operations of awareness during surgery, late psychological symptoms and post-traumatic stress disorder used in the model

Outcome	EEG monitoring	Standard monitoring	Difference
Total intravenous anaesthesia – Patients at high risk of awareness			
Awareness	10.8	45	-34.2
LPS	3.5	14.7	-11.1
PTSD	1.9	8	-6
Total intravenous anaesthesia – Patients not at high risk of awareness			
Awareness	3.8	16	-12.2
LPS	1.3	5.2	-4
PTSD	0.7	2.8	-2.1
Mixed anaesthesia– Patients at high risk of awareness			
Awareness	20.3	45	-24.7
LPS	6.6	14.7	-8.1
PTSD	3.6	8	-4.4
Mixed anaesthesia– Patients not a high risk of awareness			
Awareness	7.2	16	-8.8
LPS	2.3	5.2	-3
PTSD	1.3	2.8	-1.5
LPS Late psychological symptoms; PTSD post-traumatic stress disorder.			

4.3 Results

Separate analyses were conducted for the BIS, Entropy and Narcotrend monitors. Analyses were also conducted separately for mode of anaesthetic administration (total intravenous anaesthesia or mixed anaesthesia for patients at high risk of awareness during surgery and patients not at high risk of awareness during surgery. The cost of standard clinical monitoring varied between technologies because the cost was mainly based on the consumption of anaesthetic reported in the trials.

4.3.1 Patients at high risk of awareness receiving total intravenous anaesthesia

The cost effectiveness of EEG monitoring compared with standard clinical monitoring is shown in table 2 for patients at high risk of awareness receiving total intravenous anaesthesia.

Table 2 Cost effectiveness of EEG monitoring compared with standard clinical monitoring in patients at high risk of awareness receiving total intravenous anaesthesia

Intervention	Cost per patient (£)	Incremental cost (£)	QALYs	Incremental QALYs	ICER (£/QALY gained)
Standard clinical monitoring	24.19		–0.0011		
BIS	42.76	18.57	–0.0005	0.0007	27,345
Standard clinical monitoring	26.38	9.79	–0.0011	0.0007	14,421
E-Entropy	36.18		–0.0005		
Standard clinical monitoring	33.45	3.86	–0.0011	0.0007	5681
Narcotrend	37.31		–0.0005		

Sensitivity analyses showed that the ICERs for BIS and E-Entropy monitoring were sensitive to changes in the probability of awareness. When the probability of awareness was 0.0006, the ICER for BIS monitoring was £101,932 per QALY gained and with a probability of 0.0119 the ICER was £10,322 per QALY gained. The corresponding ICERs for E-Entropy monitoring were £56,429 per QALY gained and £4834 per QALY gained respectively.

The ICER for BIS monitoring was also sensitive to changes in the probability of late psychological symptoms and post-traumatic stress disorder, the duration of post-traumatic stress disorder, the effectiveness of the BIS module, the quality of life decrement applied to post-traumatic stress disorder and the unit cost of the sensors. Changes in the duration of late psychological symptoms or the quality of life decrement applied to late psychological symptoms had little effect on the ICER (page 136 of the diagnostics assessment report).

Changes in the quality of life decrement applied to late psychological symptoms also had little effect on the ICER for E-Entropy monitoring. In contrast to BIS monitoring, the ICER for E-Entropy monitoring was robust to changes in the unit cost of the sensors. The ICER for E-Entropy monitoring

was sensitive to changes in the relative risk of awareness and changes in the quality of life decrement applied to post-traumatic stress disorder. A decrease in the decrement increased the ICER from the base case of £14,421 per QALY gained to £21,801 per QALY gained (page 154 of the diagnostics assessment report).

The sensitivity analysis for Narcotrend monitoring showed that the ICER was robust to most changes in the parameters. However, the ICER was sensitive to changes in the probability of awareness, probability of late psychological symptoms and the decrements applied to post-traumatic stress disorder. When the probability of awareness was changed to 0.0119 and 0.0006, the ICER changed to £1,123 per QALY gained and £25,656 per QALY gained, respectively (see page 175 of the diagnostics assessment report).

4.3.2 General surgical population receiving total intravenous anaesthesia

The cost effectiveness of EEG monitoring compared with standard clinical monitoring is shown in table 3 for the general surgical population receiving total intravenous anaesthesia.

Table 3 Cost effectiveness of EEG monitoring compared with standard clinical monitoring in the general surgical population receiving total intravenous anaesthesia

Intervention	Cost per patient (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£/QALY gained)
Standard clinical monitoring	23.13	14.3	–0.0007	0.0003	45,033
BIS	37.43		–0.0004		
Standard clinical monitoring	25.32	9.89	–0.0007	0.0003	31,131
E-Entropy	35.2		–0.0004		
Standard clinical monitoring	32.39	-3.85	–0.0007	0.0003	Narcotrend dominates
Narcotrend	28.53		–0.0004		

The incremental cost of BIS monitoring is lower because of the potential to offset a reduction in the consumption of anaesthetic agents against the additional cost of BIS monitoring.

As in patients at high risk of awareness receiving total intravenous anaesthesia, the ICERs for BIS monitoring and E-Entropy monitoring were sensitive to changes in the probability of awareness. When the probability was 0.0023 the ICER for BIS monitoring was £34,842 per QALY gained and was £59,608 per QALY gained when the probability was 0.001; the corresponding ICERs for E-Entropy monitoring were £23,936 and £41,419 per QALY gained respectively. The ICERs were also sensitive to changes in the probability of developing late psychological symptoms or post-traumatic stress disorder and a reduction in the quality of life decrement applied to post-traumatic stress disorder. When the probability of late psychological symptoms was 0.48 and 0.195 the ICERs for BIS monitoring were £37,396 and £64,906 per QALY gained, respectively; the corresponding ICERs for E-Entropy were £25,678 to £45,117 per QALY gained. The ICER for E-Entropy monitoring was also sensitive to changes in the effectiveness of the E-Entropy module. Both BIS and E-Entropy monitoring were insensitive to changes in the duration of late psychological symptoms and the quality of life decrement applied to late psychological symptoms (see pages 137 and 156 of the diagnostics assessment report).

The sensitivity analysis showed that the ICER for Narcotrend monitoring in this general surgical population was robust to changes in parameters. Narcotrend monitoring dominates standard clinical monitoring by generating improved outcomes at reduced costs (see page 176 of the diagnostics assessment report).

4.3.3 Patients at high risk of awareness receiving mixed anaesthesia

The cost effectiveness of EEG monitoring compared with standard clinical monitoring is shown in table 4 for patients at high risk of awareness receiving mixed anaesthesia.

Table 4 Cost effectiveness of EEG monitoring compared with standard clinical monitoring in patients at high risk of awareness receiving mixed anaesthesia

Intervention	Cost per patient (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£/QALY gained)
Standard clinical monitoring	14.31	18.92	–0.0011	0.0005	36,126
BIS	33.23		–0.0006		
Standard clinical monitoring	19.2	10.14	–0.0011	0.0005	19,367
E-Entropy	29.35		–0.0006		
Standard clinical monitoring	38.99	4.21	–0.0011	0.0005	8,033
Narcotrend	43.2		–0.0006		

Sensitivity analyses showed that the ICERs for BIS, E-Entropy and Narcotrend monitoring were all most sensitive to changes in the probability of awareness. When the probability was 0.0119, the ICER for BIS monitoring was £16,682 per QALY gained and was £114,456 per QALY gained when the probability was 0.0006, the corresponding ICERs for E-Entropy monitoring were £7290 and £63,483 per QALY gained, respectively; the corresponding ICERs for Narcotrend monitoring were £2290 and £29,010 per QALY gained, respectively (see pages 139, 159 and 177 of the diagnostics assessment report).

Changes in the relative risk of awareness with the BIS module, probability of developing late psychological symptoms or post-traumatic stress disorder, the duration of post-traumatic stress disorder and a smaller decrement in quality of life related to post-traumatic stress disorder all led to large variations in the ICER for BIS monitoring, ranging from £23, 423 to £58, 139 per QALY gained (page 139 of the diagnostics assessment report).

The ICER for E-Entropy monitoring was also sensitive to increase in the relative risk of awareness with the Entropy module, giving an ICER of £41,635 per QALY gained (odds ratio increased from 0.45 to 0.81). As in the

population receiving total intravenous anaesthesia, the ICER was sensitive to changes in the probability of late psychological symptoms, a decrease in the probability of post-traumatic stress disorder, and a decrease in the decrement in quality of life related to post-traumatic stress disorder, but was insensitive to the decrement associated with late psychological symptoms and the duration of late psychological symptoms (page 159 of the diagnostics assessment report).

The ICER for Narcotrend monitoring was also sensitive to changes in the effectiveness of Narcotrend monitoring, the proportion of patients with late psychological symptoms who develop post-traumatic stress disorder and changes in the quality of life decrement applied to post-traumatic stress disorder. The ICER was least sensitive to changes in the quality of life decrement applied to late psychological symptoms (page 177 of the diagnostics assessment report).

4.3.4 General surgical population receiving mixed anaesthesia

The cost effectiveness of EEG monitoring compared with standard clinical monitoring is shown in table 5 for the general surgical population receiving mixed anaesthesia.

Table 5 Cost effectiveness of EEG monitoring compared with standard clinical monitoring in the general surgical population receiving mixed anaesthesia

Intervention	Cost per patient (£)	Incremental Cost (£)	QALYs	Incremental QALYs	ICER (£/QALY gained)
Standard clinical monitoring	13.25	16.23	–0.0007	0.0003	61,869
BIS	29.48		–0.0004		
Standard clinical monitoring	18.14	4.99	–0.0007	0.0003	19,000
E-Entropy	23.12		–0.0004		
Standard clinical monitoring	37.93	-1.74	–0.0007	0.0003	Narcotrend dominates
Narcotrend	36.18		–0.0004		

Sensitivity analysis showed that the ICER for BIS monitoring in this population was most sensitive to increase in the probability of late psychological symptoms resulting in an ICER of £84,329 per QALY gained. Again, the ICER was sensitive to changes in the probability of awareness with ICERs of £49,437 and £78,532 per QALY gained for probabilities of 0.0023 and 0.001 respectively. The ICER was also sensitive to changes in the relative risk of awareness with the BIS monitor, changes in the probability of developing post-traumatic stress disorder, the duration of post-traumatic stress disorder and the unit costs of the sensors (page 140 of the diagnostics assessment report).

For E-Entropy monitoring, sensitivity analyses showed that the largest variation in the ICER from the base case of £19,000 per QALY gained was caused by changes in sevoflurane consumption, resulting in ICERs of £6494 and £31,567 per QALY gained. When the probability of awareness was 0.0023 and 0.001 the ICERs were £14, 881 and £24, 521 per QALY gained, respectively.

The ICER was also sensitive to changes in the probability of late psychological symptoms or post-traumatic stress disorder, a reduction in the quality of life decrement applied to post-traumatic stress disorder and changes in the unit cost of the sensors (page 160 of the diagnostics assessment report).

The sensitivity analysis showed that the ICER for Narcotrend monitoring in this population was generally robust to changes in the parameters. However, the ICER was sensitive to changes in the consumption of desflurane resulting in an ICER of £2534 per QALY gained.

4.3.5 Scenario analyses for BIS monitoring

Scenario analyses are described in more detail on page 141 of the diagnostics assessment report. There were no robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting so scenario analyses were performed. The incremental costs for BIS monitoring were

reduced because of reductions in the costs of treating nausea and vomiting, but this changed the ICERs insignificantly for all population groups.

There is uncertainty about the incidence of awareness during surgery and the value used in the base-case analysis was lower than the values frequently quoted for the high-risk population. The estimate in the base case for the high-risk population (0.45%) was from pooled values across studies and excluded two outlying studies. Scenario analysis was performed using an estimate of 1% (reported for certain types of surgery such as cardiac and caesarean section) for the probability of awareness. This resulted in a doubling of the QALY gains associated with BIS monitoring and a halving of the ICERs for the high-risk population. For the general population, an increase in the probability of awareness to 0.99% resulted in a 3- to 4-fold increase in the QALY gain associated with BIS monitoring and a substantial reduction in the ICERs. A reduction in the probability of awareness to 0.007% resulted in high ICERs.

Scenario analysis was performed to investigate the impact of the assumed number of patients per device year (1000 patients) in the base-case analysis. It showed that the assumption only substantially affected the ICERs at low patient numbers (less than 500 patients).

To investigate the impact of the quality of life decrement applied to post-traumatic stress disorder in the base-case analysis, scenario analysis was performed using an increased utility decrement of 0.5 and 0.75 for both the high-risk population and the general population. For both populations there was a substantial reduction in the ICERs when the quality of life decrement applied to post-traumatic stress disorder was increased.

4.3.6 Scenario analyses for E-Entropy monitoring

Scenario analyses are described in more detail on page 161 of the diagnostics assessment report. There were no robust data to estimate the effect of E-Entropy monitoring on post-operative nausea and vomiting so scenario analyses were performed. The ICERs were insensitive to changes in the probability of post-operative nausea and vomiting for both populations receiving total intravenous anaesthesia and the high-risk population receiving

mixed anaesthesia. For the general population receiving mixed anaesthesia there was a slight reduction in the ICER.

There was uncertainty about the incidence of awareness during surgery and the value used in the base-case analysis (from pooled values across studies) was lower than the 1% quoted in some studies for the high-risk population. Scenario analysis was performed using the higher value of 1% for the probability of awareness and this showed the ICER was sensitive to changes in this parameter. Threshold analysis showed that for patients receiving total intravenous anaesthesia, E-Entropy monitoring was cost effective if the probability of awareness was greater than 0.192% at a maximum acceptable ICER of £30,000 per QALY gained. For a lower maximum acceptable ICER of £20,000 per QALY gained, the probability of awareness would have to be greater than 0.315% for E-Entropy monitoring to be cost effective. For patients receiving mixed anaesthesia, sensitivity analysis showed that E-Entropy monitoring was cost effective if the probability of awareness was greater than 0.098% at a maximum acceptable ICER of £30,000 per QALY gained and greater than 0.196% for a maximum acceptable ICER of £20,000 per QALY gained.

Scenario analysis was performed to investigate the impact of the assumed number of patients per device year (1000 patients) in the base-case analysis. It showed that the assumption only substantially affected the ICERs at low patient numbers (less than 500 patients).

To investigate the impact of the quality of life decrement applied to post-traumatic stress disorder in the base-case analysis, scenario analysis was performed using an increased utility decrement of 0.5 and 0.75 for both the high-risk population and the general population. For both populations there was a substantial reduction in the ICERs when the quality of life decrement applied to post-traumatic stress disorder was increased.

4.3.7 Scenario analyses for Narcotrend monitoring

Scenario analyses are described in more detail on page 179 of the diagnostics assessment report. There were no robust data to estimate the

effect of Narcotrend monitoring on post-operative nausea and vomiting so scenario analyses were performed. The ICERs were insensitive to changes in the probability of post-operative nausea and vomiting for both risk groups receiving total intravenous anaesthesia and the general population receiving mixed anaesthesia. For the high-risk population receiving mixed anaesthesia there was a slight reduction in the ICER.

There was uncertainty about the incidence of awareness during surgery and the value used in the base-case analysis (from pooled values across studies) was lower than the 1% quoted in some studies for the high-risk population. Scenario analysis was performed using the higher value of 1% for the probability of awareness and this showed the ICERs were sensitive to changes in this parameter for the high-risk population receiving total intravenous anaesthesia or mixed anaesthesia. The ICERs decrease substantially when the probability of awareness increases to 1%. For the general population, Narcotrend monitoring dominates standard clinical monitoring when the probability of awareness is 1% and 0.07%.

Scenario analysis was performed to investigate the impact of the assumed number of patients per device year (1000 patients) in the base-case analysis. It showed that the assumption only substantially affected the ICERs at low patient numbers (less than 500 patients).

To investigate the impact of the quality of life decrement applied to post-traumatic stress disorder in the base-case analysis, scenario analysis was performed using an increased utility decrement of 0.5 and 0.75 for both the high-risk population and the general population. For the high-risk population there was a substantial reduction in the ICERs when the quality of life decrement applied to post-traumatic stress disorder was increased. For the general population Narcotrend monitoring dominated standard clinical monitoring when the quality of life decrement applied to post-traumatic stress disorder was increased.

5 Issues for consideration

Although the modelling shows ICERs at acceptable levels for Narcotrend and E-Entropy in most cases, these results were based on the use of data from BIS for estimating the impacts on awareness during surgery and its sequelae and for long term complications of anaesthesia overdosing. No robust evidence was identified on the effect of the E-Entropy or Narcotrend monitors on awareness during surgery or post-operative cognitive dysfunction so the effect estimates derived for BIS were applied to E-Entropy and Narcotrend in the modelling. Also evidence on long-term cognitive dysfunction was limited to one study using BIS on patients over 60. This study was used to estimate post-operative cognitive dysfunction for all three modalities and it was assumed that any difference between standard monitoring and the modality evaluated was restricted to those over 60.

There is a large amount of heterogeneity between the studies included in the systematic review. In particular, the effectiveness of standard clinical monitoring varies both in studies of a single monitor and between monitors. This results in an inconsistent baseline and a large amount of uncertainty.

Each depth of anaesthesia monitor has been separately compared with standard clinical monitoring. There are no data available to permit an direct accurate comparison of the monitors. The differences in the results for BIS, Narcotrend and E-Entropy arise from a combination of cost differences and differences in the reduction in anaesthesia use and recovery time from the different studies. Because of the availability of evidence, there is extensive analysis of the outcomes (such as awareness during surgery) associated with underdosing of anaesthesia but less analysis of the longer term outcomes associated with overdosing of anaesthesia (for example, cognitive dysfunction).

Because awareness during surgery is such a rare event, there is no robust evidence to show if the reduction in the consumption of anaesthetic through depth of anaesthesia monitoring could inadvertently increase the risk of awareness during surgery.

It is uncertain if the costs associated with time in recovery were included in the cost-effectiveness analysis.

6 Equality considerations

The clinical effectiveness of depth of anaesthesia monitors may be affected when monitoring patients with neurological disorders, trauma or their sequelae, or people taking psychoactive medication, high-dose beta blockers or anti-retroviral drugs. This may have equality implications for people protected by equalities legislation.

7 Summary

The systematic review found that monitoring with the BIS, E-Entropy or Narcotrend monitors was associated with lower general anaesthetic consumption and shorter recovery times. The use of the BIS monitor was also associated with overall lower rates of explicit awareness during surgery (limited to patients at high risk of awareness, and non-significant effects in the subgroup receiving only inhaled anaesthetic). Monitoring with the E-Entropy and the Narcotrend monitors did not consistently affect the incidence of awareness during surgery although as the trials were not designed to detect this, it is likely that the sample sizes were insufficient to detect these rare events. There is uncertainty in the interpretation of the results of the systematic review for all the monitors because not all of the outcomes were adequately statistically powered and there was a large amount of heterogeneity. There was also variation between the trials in terms of patient characteristics and surgical procedures.

The three separate cost-effectiveness analyses for BIS, E-Entropy and Narcotrend monitoring were compared with standard clinical monitoring for two modes of anaesthetic administration (total intravenous anaesthesia or mixed anaesthesia) in two populations (at high risk of awareness or general risk of awareness). Overall, the economic evaluation indicates that, for patients receiving general anaesthesia who are at general risk of awareness, the additional costs of depth of anaesthesia monitoring may be offset by reductions in the consumption of anaesthetic. However, the size of these

savings may not fully offset the additional cost. Because awareness events are rare, the cost savings associated with the avoidance of post-traumatic stress disorder are also unlikely to offset the full additional cost. The additional costs of depth of anaesthesia monitoring are less dependent on the acquisition cost of the monitor than the cost of consumables. In particular, the cost of the disposable sensors appears to be a key determinant. The baseline risk of awareness during surgery and the effect size in terms of avoiding awareness are also key determinants of cost effectiveness.

There is substantial uncertainty in the analyses owing to the weakness of the evidence base for most of the outcomes included in the model. No robust evidence was identified on the effectiveness of Entropy or Narcotrend in avoiding awareness during surgery or post-operative cognitive dysfunction so in the absence of such evidence the effect estimates derived for BIS were applied. There is some evidence of reduced anaesthetic drug consumption associated with the use of the depth of anaesthesia monitors, although for some monitors the evidence is inconclusive.

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Appendix A: Sources of evidence considered in the preparation of the overview

A. The diagnostics assessment report for this assessment was prepared by Southampton Health Technology Assessments Centre (SHTAC):

- Shepherd J, Jones J, Frampton G et al. Depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend) Health Technology Assessment 2012

B. The following organisations accepted the invitation to participate in this assessment as stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

I. Manufacturers/sponsors:

Technology(ies) under consideration

- Covidien
- GE Healthcare
- MT MonitorTechnik

Comparator(s)

- None

Other

- Medical Device Management Ltd.
- Draeger Medical UK Ltd.
- Masimo International

II. Professional/specialist and patient/carer groups:

- Association of Anaesthetists of Great Britain and Ireland (AAGBI)
- ICU Steps
- Royal College of Anaesthetists
- Royal College of Nursing
- Royal College of Paediatrics and Child Health
- UK Society for Intravenous Anaesthesia