NICE National Institute for Health and Care Excellence

NICE guidance

Depth of anaesthesia monitors – Bispectral Index (BIS), E-Entropy and Narcotrend-Compact M

HealthTech guidance

Published: 21 November 2012

www.nice.org.uk/guidance/htg292

Your responsibility

This guidance represents the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, healthcare professionals are expected to take this guidance fully into account, and specifically any special arrangements relating to the introduction of new interventional procedures. The guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the Yellow Card Scheme.

Commissioners and/or providers have a responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties. Providers should ensure that governance structures are in place to review, authorise and monitor the introduction of new devices and procedures.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

This guidance replaces DG6.

1 Recommendations

1.1 The use of electroencephalography (EEG)-based depth of anaesthesia monitors is recommended as an option during any type of general anaesthesia in patients considered at higher risk of adverse outcomes. This includes patients at higher risk of unintended awareness and patients at higher risk of excessively deep anaesthesia. The Bispectral Index (BIS) depth of anaesthesia monitor is therefore recommended as an option in these patients.

1.2 The use of EEG-based depth of anaesthesia monitors is also recommended as an option in all patients receiving total intravenous anaesthesia. The BIS monitor is therefore recommended as an option in these patients.

1.3 Although there is greater uncertainty of clinical benefit for the E-Entropy and Narcotrend-Compact M depth of anaesthesia monitors than for the BIS monitor, the Committee concluded that the E-Entropy and Narcotrend-Compact M monitors are broadly equivalent to BIS. These monitors are therefore recommended as options during any type of general anaesthesia in patients considered at higher risk of adverse outcomes. This includes patients at higher risk of unintended awareness and patients at higher risk of excessively deep anaesthesia. The E-Entropy and Narcotrend-Compact M monitors are also recommended as options in patients receiving total intravenous anaesthesia.

1.4 Anaesthetists using EEG-based depth of anaesthesia monitors should have appropriate training and experience with these monitors and understand the potential limitations of their use in clinical practice.

Patients who are considered at higher risk of unintended awareness during general anaesthesia include patients with high opiate or high alcohol use, patients with airway problems, and patients with previous experience of accidental awareness during surgery. The risk of unintended awareness is also raised by the use of concomitant muscle relaxants. Older patients, patients with comorbidities and those undergoing certain types of surgery are also considered at higher risk of unintended awareness. This is because they are at greater risk of haemodynamic instability during surgery. In these patients, lower levels of anaesthetic are often used to prevent adverse effects on the cardiovascular system and these levels can be inadequate.

Patients who are considered at higher risk of excessively deep levels of anaesthesia include older patients, patients with liver disease, patients with a high body mass index (BMI), and patients with poor cardiovascular function.

Patients receiving total intravenous anaesthesia are not considered at higher risk of adverse outcomes from general anaesthesia than patients receiving inhaled anaesthesia. The use of EEG-based depth of anaesthesia monitors has been recommended in patients receiving total intravenous anaesthesia because it is cost effective and because it is not possible to measure end-tidal anaesthetic concentration in this group.

2 The technologies

2.1 The BIS monitor (Covidien), E-Entropy monitor (GE Healthcare) and Narcotrend-Compact M monitor (MT MonitorTechnik) are EEG-based monitors that are used in combination with standard clinical monitoring and clinical skills to indicate the patient's response to anaesthetic drugs (hereafter referred to as depth of anaesthesia) during surgery.

2.2 Other manufacturers have licensed the BIS (or BISx) technology from Covidien in order to produce BIS modules that are compatible with their own anaesthesia systems.

3 Clinical need and practice

The problem addressed

3.1 EEG-based depth of anaesthesia monitors are designed to indicate the probability of consciousness with explicit recall in patients receiving general anaesthetics, and to aid the tailoring of anaesthetic dose to the individual patient to avoid inadequate or excessively deep levels of anaesthesia. Measuring a patient's response to anaesthesia is important clinically because individual variation in response to anaesthetics can occasionally lead to inadequate or excessively deep levels of anaesthesia. An inadequate level of anaesthesia can result in patient awareness during surgery, which can cause post-traumatic stress disorder in some patients. Conversely, an excessively deep level of anaesthesia can result in prolonged recovery and has been linked to an increased risk of postoperative adverse outcomes, including myocardial infarction, stroke and cognitive dysfunction in older patients.

3.2 The aim of this evaluation is to determine the clinical and cost effectiveness of 3 depth of anaesthesia monitors, in combination with standard clinical monitoring, in patients receiving general anaesthesia.

The condition

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

3.4 Some common adverse outcomes of general anaesthesia include nausea, headaches and dizziness. Less common adverse outcomes include neurological and cardiovascular morbidity, and unintended patient awareness and recall. Most studies suggest that between 1 and 2 people in 1,000 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 clinical depression, anxiety, nightmares, flashbacks and, in some cases, severe post-traumatic stress disorder.

3.5 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. 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.

3.6 Anaesthetic agents can affect the body's physiology, in particular, the cardiovascular system. Adverse outcomes of excessively deep general anaesthesia include prolonged recovery, particularly in people with a high BMI. In severe cases or in at-risk patient groups (for example, older patients, patients with liver disease, and patients with poor cardiovascular function), excessively deep anaesthesia can result in haemodynamic instability and respiratory complications (which can be fatal without cardiorespiratory support). Inappropriately deep anaesthesia has also been linked to an increased risk of post-operative complications such as myocardial infarction and stroke in older patients. There is some evidence to suggest a link between longer term morbidity (for example, cognitive dysfunction) and mortality, and the depth of anaesthesia.

3.7 Groups of patients who are considered at higher risk of unintended awareness during general anaesthesia include patients with high opiate or high alcohol use, patients with airway problems, and patients with previous experience of accidental awareness during surgery. The risk of unintended awareness is also raised by the concomitant use of muscle relaxants, particularly with total intravenous anaesthesia. Older patients, patients with comorbidities and those undergoing certain types of surgery are also considered at higher risk of unintended awareness because they are at greater risk of haemodynamic instability during surgery. Therefore, lower levels of anaesthetic are often used to prevent adverse effects on the cardiovascular system, which can result in these patient groups receiving inadequate levels of anaesthesia.

The diagnostic and care pathways

3.8 Before general anaesthesia, the anaesthetist interviews the patient and reviews the 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 into or out of the operating theatre.

3.9 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) may be carried out before moving the patient into the operating theatre.

3.10 During surgery, other drugs may be given with the general anaesthesia. These may include analgesics, regional anaesthesia, antibiotics, anti-emetic drugs and muscle relaxants. In current NHS clinical practice, a patient's response to anaesthesia during surgery is assessed by clinical observation of signs such as excessive tear formation (lacrimation), sweating, pupillary size and reactivity, 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 estimate the amount of oxygen in the blood; a device to measure the patient's temperature; a device to monitor end-tidal anaesthetic concentration (for inhaled anaesthesia) and provide a minimum alveolar concentration (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 be used for some patients or certain types of surgery.

Be aware that some pulse oximeters can underestimate or overestimate oxygen saturation levels, especially if the saturation level is borderline. Overestimation has been reported in people with dark skin. See also the NHS England Patient

Safety Alert on the risk of harm from inappropriate placement of pulse oximeter probes.

3.11 After surgery, the administration of anaesthetic is stopped, muscle relaxant drugs are reversed (if used) and analgesics are given as appropriate. Patients are extubated (if necessary) before being moved to the recovery room and regaining consciousness. Once they have recovered from the anaesthetic and meet the criteria for discharge after anaesthesia, they can be discharged from recovery to a general ward. When patients do not meet the discharge criteria, they remain in the recovery room 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.

4 The diagnostic tests

The interventions

Bispectral Index

4.1 The BIS system uses a disposable 4-electrode 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 to 60; this range indicates a low probability of awareness with recall. The BIS sensors are only compatible with BIS modules. Other manufacturers have licensed the BIS (or BISx) technology in order to produce BIS modules that are compatible with their own anaesthesia systems. The manufacturer estimates that 100% of all UK operating theatres would be compatible with the BIS system.

E-Entropy

4.2 The E-Entropy monitor measures irregularity in spontaneous brain and facial muscular activity. It uses a proprietary algorithm to process EEG and frontal electromyography data to produce 2 values that indicate the depth of anaesthesia, response entropy (RE) and state entropy (SE).

4.3 Highly irregular signals with variation of wavelength and amplitude over time produce high entropy values 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 suppression of brain electrical activity and a low probability of recall. 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 target range for entropy values is 40 to 60. RE and SE values near 40 indicate a low probability of awareness with recall.

4.4 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 using a disposable sensor with 3 electrodes that are attached to the patient's forehead and a sensor cable that connects the sensor to the Entropy module. The sensors are not compatible with other systems. 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.

Narcotrend-Compact M

4.5 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 automatic classification functions were developed from visual classification of 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. Generic sensors can be used with Narcotrend-Compact M monitors.

The comparator: standard clinical monitoring

4.6 The combination of standard clinical observation (of pupillary size and reactivity, excessive tear formation, sweating and patient movement) and measurement of 1 or more clinical markers such as pulse, blood pressure and end-tidal anaesthetic gas concentration (for inhaled anaesthesia) constitutes standard clinical monitoring and is the comparator for this assessment.

5 Outcomes

The diagnostics advisory committee considered evidence from a number of sources but primarily the assessment performed by the External Assessment Group.

How outcomes were assessed

5.1 The assessment consisted of a systematic review of the evidence on clinical-effectiveness data for the 3 depth of anaesthesia monitors compared with standard clinical monitoring. The outcome measures included consumption of anaesthetic agents, time to extubation, time to discharge from the recovery room, probability of awareness during surgery, patient distress and other sequelae resulting from awareness during surgery, morbidity including post-operative cognitive dysfunction, and mortality.

Clinical effectiveness

Bispectral Index

5.2 A Cochrane review on 'Bispectral Index for improving anaesthetic delivery and post-operative recovery' provided a basis for assessing the clinical effectiveness of BIS. It included 31 randomised controlled trials of BIS monitoring compared with standard clinical practice. All of the trials included in the Cochrane review were conducted in adults. The external assessment group identified 11 randomised controlled trials that were published after the Cochrane review and compared the clinical effectiveness of the BIS monitor with standard clinical monitoring. Five of these trials were conducted in children aged 2 to 18 years. Two of the trials were conducted in populations with known risk factors for awareness during surgery (for example, patients undergoing cardiac or airway surgery). These 11 trials were used to supplement the Cochrane review. 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 3 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 7 of the trials.

5.3 A total of 6 trials identified by the external assessment group reported awareness during surgery as an outcome and 3 of these trials reported this as the primary outcome. The 3 trials that did not report awareness as the primary outcome had no cases of awareness during surgery. These 3 trials were not designed to detect awareness during surgery, and it is likely that the sample sizes were insufficient to detect this uncommon outcome. In the 3 trials that did report awareness as the primary outcome, there were 29 cases of confirmed or possible awareness during surgery with BIS monitoring and 30 cases with the comparators used in the studies. One trial, monitoring inhaled anaesthesia in patients classified as being 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 clinical monitoring, which included a structured protocol with audible alarms for monitoring end-tidal anaesthetic concentration (n=2852). This difference was not statistically significant. The use of structured protocols is not considered part of standard clinical monitoring in the NHS. A second trial, in 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 standard clinical monitoring group (n=2309). The lower incidence of confirmed awareness in the group with BIS monitoring was statistically significant. A third trial, monitoring inhaled or intravenous anaesthesia in patients not classified at greater risk, reported 2 cases of awareness during surgery in the group with BIS monitoring (n=67) compared with 1 case in the group with standard clinical monitoring (n=61). Statistical significance was not reported. This trial measured awareness with explicit recall using a modified Brice interview and awareness with implicit recall using a word recognition test. The sample size of this study was small and may have contributed to the inconclusive results.

5.4 The Cochrane review on BIS included a meta-analysis of awareness during surgery with recall, which included 4 trials in patients at high risk of awareness during surgery. This meta-analysis was updated by the external assessment

group to include 2 further trials in patients at high risk of awareness during surgery. After the addition of these 2 trials, 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.

5.5 Six trials identified by the external assessment group reported anaesthetic consumption as an outcome and 2 of these reported it 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 3 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 2 groups. The third trial reported a 25.3% reduction in the consumption of intravenous anaesthetic (propofol) with BIS monitoring compared with standard clinical monitoring. No statistical significance was reported in the trial.

5.6 The Cochrane review of 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 External Assessment Group, the mean difference (in MAC equivalents) 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 mg/kg/h to −1.33 mg/kg/h but remained statistically significant.

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

5.8 Five trials identified by the external assessment group reported the time to discharge from the recovery room as a secondary outcome, and 4 of these trials were conducted in children. All of the trials showed that the time to discharge was shorter by 6.7 to 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 varied across the trials. One trial reported the time to discharge from the end of surgery and 2 others reported time to discharge from the end of general anaesthesia.

5.9 In the Cochrane review, 12 trials were included in the meta-analysis of the time to discharge from the recovery room. The mean difference in the Cochrane review was −7.63 minutes in favour of BIS. The external assessment group did not update the Cochrane review for this outcome because of heterogeneity between studies.

5.10 One trial conducted in children receiving inhaled anaesthesia reported post-operative nausea and vomiting as a secondary outcome. There was no significant difference between BIS monitoring and standard clinical monitoring in the number of children with nausea (n=5 [10%] and n=6 [11%] respectively, p=0.95) or with vomiting (n=2 [4%] and n=3 [6%] respectively, p=0.88). The Cochrane review did not report post-operative nausea and vomiting.

5.11 The evidence on long-term cognitive dysfunction following general anaesthesia was limited to 1 study (reported in a conference abstract) of patients over 60 years of age. This study reported a reduction in post-operative cognitive dysfunction at 7 days and 3 months with BIS monitoring, although the difference at 7 days was not statistically significant.

E-Entropy

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

5.13 The method of administering general anaesthesia varied across trials. Two trials used inhaled anaesthetic (sevoflurane) and 3 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 1 trial used muscle relaxants.

5.14 There was 1 case of awareness during surgery in the 6 trials that reported this outcome. This occurred in the standard clinical monitoring group. Sample sizes were small in all of the trials, so uncommon events such as awareness during surgery may not have occurred or have been detected.

5.15 Four trials showed a statistically significant reduction in the consumption of inhaled anaesthetic with E-Entropy monitoring compared with standard clinical monitoring, although 1 of these trials showed no reduction in the total amount of anaesthetic consumed. By contrast, no statistically significant reduction in the consumption of intravenous anaesthetic was found in a trial reporting the consumption of intravenous anaesthetic as a primary outcome. However, 2 trials that reported the consumption of intravenous anaesthesia as a secondary outcome did show lower propofol consumption with E-Entropy monitoring compared with standard clinical monitoring that was statistically significant.

5.16 Three trials reported time to extubation as a secondary outcome. All showed that time to extubation was shorter by approximately 3 to 4 minutes with E-Entropy monitoring compared with standard clinical monitoring. Two of these trials reported this reduction in time to extubation as statistically significant. Two trials reported that the time to discharge from the operating room to the recovery room was reduced by approximately 3 to 4 minutes with E-Entropy monitoring compared with standard clinical monitoring. Both trials reported that this result was statistically significant. Only 1 trial reported the time to discharge from the recovery room. The group with E-Entropy monitoring was discharged sooner than the group with standard clinical monitoring, but the difference was not statistically significant.

5.17 One trial conducted in patients receiving intravenous anaesthesia reported post-operative nausea and vomiting as a secondary outcome. There was no statistically significant difference in the number of patients with nausea and vomiting in the group with E-Entropy monitoring and in the group with standard clinical monitoring.

Narcotrend-Compact M

5.18 Four randomised controlled trials comparing the clinical effectiveness of the

Narcotrend-Compact M monitor with standard clinical monitoring were included in the systematic review conducted by the External Assessment Group. All of these were conducted in adults. None reported risk factors in the study populations for awareness during surgery.

5.19 The method of administering general anaesthesia varied across trials. Three trials used total intravenous anaesthesia (propofol-remifentanil or propofol-fentanyl) and 1 other trial had a mix of patients receiving intravenous anaesthesia and inhaled anaesthetic (propofol-remifentanil and desflurane-remifentanil) for general anaesthesia. Three trials used muscle relaxants.

5.20 There were no cases of awareness during surgery in any of the trials reporting the clinical effectiveness of the Narcotrend-Compact M monitor.

5.21 Of 3 trials that reported consumption of the anaesthetic propofol, 2 showed a statistically significant reduction in consumption with Narcotrend-Compact M monitoring compared with standard clinical monitoring. The third trial showed no difference in propofol consumption between the 2 groups.

5.22 In 1 trial that reported time to extubation as a primary outcome, no difference was found between the group with Narcotrend-Compact M monitoring and the group with standard clinical monitoring. Two trials that reported time to extubation as a secondary outcome showed a statistically significant reduction of 1.4 to 6 minutes with Narcotrend-Compact M monitoring compared with standard clinical monitoring.

5.23 Two trials reported a statistically significant reduction in the time to arrival at the recovery room in the group with Narcotrend-Compact M monitoring compared with the group with standard clinical monitoring.

Cost effectiveness

5.24 A systematic review of the evidence on cost effectiveness for the 3 technologies was undertaken by the External Assessment Group. One study was identified that evaluated the cost effectiveness of standard clinical monitoring in combination with BIS monitoring compared with standard clinical monitoring alone. 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 in combination with BIS monitoring and 0.18% was used for standard clinical monitoring alone. The study concluded that the addition of BIS monitoring to standard clinical monitoring was not cost effective. However, the study did not include health-related quality of life and its methodology was of uncertain quality.

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

5.26 An economic model was developed by the external assessment group 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 3 technologies. No analyses were conducted to directly compare the technologies.

5.27 A decision tree model was developed to evaluate the outcomes and costs resulting from the use of depth of anaesthesia monitors as opposed to standard clinical monitoring alone. The relevant clinical outcomes included in the model were those associated with excessively deep levels and inadequate levels of general anaesthesia in the general surgical population and the population at high risk of awareness. Specifically, these were the risk of experiencing short-term adverse outcomes (such as post-operative nausea and vomiting) and long-term adverse outcomes (such as post-traumatic stress disorder and post-operative cognitive dysfunction), and the risk of experiencing awareness during surgery.

5.28 The model was also used to estimate the costs associated with depth of anaesthesia monitoring and the costs of treating short- and long-term adverse outcomes. It was assumed that the costs of monitoring clinical signs such as blood pressure and heart rate were common to all surgery with general anaesthesia with and without depth of anaesthesia 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 adverse outcomes

related to anaesthesia and costs of managing long-term sequelae of awareness during surgery. The costs associated with post-operative nausea and vomiting were also included. No impact of short-term adverse outcomes on quality of life was included in the model because, by definition, these are expected to be of short duration.

5.29 Three separate models were developed, 1 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 standard clinical monitoring (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.

5.30 For each monitor, 4 analyses were performed; 2 each for the population at general risk of adverse outcomes from anaesthesia and for the population at high risk of adverse outcomes from anaesthesia. For each of the 2 populations, 2 analyses were performed; 1 for patients receiving total intravenous anaesthesia and 1 for a general mix of patients regardless of the type of anaesthesia.

5.31 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-Compact M). Sensor costs varied more widely, with costs per patient of £14.08 for BIS, £8.68 for E-Entropy and £0.56 for Narcotrend-Compact M.

5.32 The cost-effectiveness estimates in the following sections were, in most cases, derived using data from BIS monitoring for estimating the impact on awareness during surgery and its sequelae, and for long-term adverse outcomes of anaesthesia overdosing. No robust evidence was identified on the effect of the E-Entropy or Narcotrend-Compact M monitors on awareness during surgery and its sequelae, or for long-term adverse outcomes of anaesthesia overdosing. Therefore, the effect estimates derived from studies using the BIS monitor were applied to E-Entropy and Narcotrend-Compact M in the modelling.

Patients at high risk of adverse outcomes from anaesthesia receiving total intravenous anaesthesia

5.33 The base-case analysis for patients at high risk of adverse outcomes from anaesthesia receiving total intravenous anaesthesia resulted in incremental cost-effectiveness ratios (ICERs) of £21,940, £14,421 and £5681 per QALY gained for BIS, E-Entropy and Narcotrend-Compact M monitoring respectively, compared with standard clinical monitoring alone.

5.34 Sensitivity analyses showed that the ICERs for BIS, E-Entropy and Narcotrend-Compact M monitoring were sensitive to changes in the probability of awareness during surgery. When the probability of awareness was 0.0006, the ICER for BIS monitoring was £82,903 per QALY gained and, with a probability of 0.0119, the ICER was £8027 per QALY gained compared with standard clinical monitoring alone. The corresponding ICERs for E-Entropy monitoring were £56,429 per QALY gained and £4834 per QALY gained respectively. The corresponding ICERs for Narcotrend-Compact M monitoring were £25,656 per QALY gained and £1123 per QALY gained respectively.

5.35 The ICER for BIS monitoring was also sensitive to changes in the probability and 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.

5.36 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.

5.37 The sensitivity analysis for Narcotrend-Compact M 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 and the decrement applied to post-traumatic stress disorder.

Patients at general risk of adverse outcomes from anaesthesia receiving total intravenous anaesthesia

5.38 The base-case analysis for patients at general risk of adverse outcomes from anaesthesia receiving total intravenous anaesthesia resulted in ICERs of £33,478 and £31,131 per QALY gained for the use of BIS and E-Entropy monitors respectively, compared with standard clinical monitoring alone. Monitoring with the Narcotrend-Compact M monitor dominated standard clinical monitoring in this population (that is, it was more effective and less costly than standard clinical monitoring).

5.39 As in patients at high risk of adverse outcomes from anaesthesia 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 £25,778 per QALY gained compared with standard clinical monitoring alone. When the probability was 0.001, the ICER increased to £44,491 per QALY gained. 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 post-traumatic stress disorder and the quality-of-life decrement applied to post-traumatic stress disorder. The ICER for E-Entropy monitoring was also sensitive to changes in the effectiveness of the E-Entropy module.

5.40 The sensitivity analysis showed that the ICER for Narcotrend-Compact M monitoring in this general risk population was robust to changes in parameters. Narcotrend-Compact M monitoring dominated standard clinical monitoring by generating improved outcomes at reduced costs.

Patients at high risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia

5.41 The base-case analysis for patients at high risk of adverse outcomes from anaesthesia receiving intravenous or inhaled anaesthesia resulted in ICERs of £29,118, £19,367 and £8,033 per QALY gained for the use of BIS, E-Entropy and Narcotrend-Compact M monitors respectively, compared with standard clinical monitoring alone.

5.42 Sensitivity analyses showed that the ICERs for BIS, E-Entropy and Narcotrend-Compact M monitoring were most sensitive to changes in the probability of awareness. When the probability was 0.0119, the ICER for BIS monitoring compared with standard clinical monitoring alone was £11,591 per QALY gained, rising to £93,139 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-Compact M monitoring were £2290 and £29,010 per QALY gained respectively.

5.43 Changes in the relative risk of awareness with the BIS module, probability of developing post-traumatic stress disorder, the duration of post-traumatic stress disorder and the decrement in quality of life applied to post-traumatic stress disorder all led to large variations in the ICER for BIS monitoring, ranging from £22,207 to £61,433 per QALY gained compared with standard clinical monitoring alone.

5.44 The ICER for E-Entropy monitoring was also sensitive to an increase in the relative risk of awareness with the Entropy module, giving an ICER of £41,635 per QALY gained compared with standard clinical monitoring alone when the odds ratio was 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 post-traumatic stress disorder and the decrement in quality of life applied to post-traumatic stress disorder.

5.45 The ICER for Narcotrend-Compact M monitoring was also sensitive to changes in the effectiveness of the Narcotrend-Compact M monitor, the proportion of patients who develop post-traumatic stress disorder and the quality-of-life decrement applied to post-traumatic stress disorder.

Patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia

5.46 The base-case analysis for patients at general risk of adverse outcomes from anaesthesia receiving intravenous or inhaled anaesthesia resulted in ICERs of £47,882 and £19,000 per QALY gained for the use of BIS and E-Entropy monitors respectively, compared with standard clinical monitoring alone. Monitoring with

the Narcotrend-Compact M monitor dominated standard clinical monitoring in this population (that is, it was more effective and less costly than standard clinical monitoring).

5.47 Sensitivity analysis showed that the ICER for BIS monitoring in this population was sensitive to changes in the probability of awareness with ICERs of £38,163 and £60,911 per QALY gained for probabilities of 0.0023 and 0.001 respectively, compared with standard clinical monitoring alone. 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.

5.48 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, with ICERs ranging from £6494 to £31,567 per QALY gained, compared with standard clinical monitoring alone. When the probability of awareness was 0.0023 and 0.001 the ICERs were £14,881 and £24,521 per QALY gained respectively, compared with standard clinical monitoring alone.

5.49 The ICER for E-Entropy monitoring was also sensitive to changes in the probability of post-traumatic stress disorder, the decrement in quality of life applied to post-traumatic stress disorder and changes in the unit cost of the sensors.

5.50 The sensitivity analysis showed that the ICER for Narcotrend-Compact M monitoring in this population was generally robust to changes in the parameters. However, the ICER was sensitive to a change in the consumption of desflurane (−0.156 to −0.056), resulting in an ICER of £2534 per QALY gained compared with standard clinical monitoring alone.

5.51 Scenario analyses were performed to investigate the impact of varying the assumed number of patients per monitor per year (1000 patients) in the base-case analyses. These analyses showed that the number of patients per monitor only had a substantial effect on the ICERs at low patient numbers (less than 500 patients). This applied for all 3 monitors.

6 Considerations

6.1 The Committee considered the heterogeneity and uncertainty in the studies and the resulting ICERs. It concluded that the large degree of heterogeneity and uncertainty arose mainly from the individual response to anaesthesia, the case mix and the variation in administering anaesthesia in clinical practice.

6.2 The Committee was advised that population groups considered to be at high risk of adverse events from anaesthesia varied with changes in anaesthesia practice, but that the type of surgery, patient's age, BMI and comorbidities were known risk factors.

6.3 The Committee was advised that post-traumatic stress disorder following awareness during surgery can be severe and have far-reaching consequences for the patient's quality of life beyond those considered within the health context (for example, marital breakdown and loss of employment). The Committee also noted that people who experience awareness during surgery can become averse to any contact with the healthcare system and may not seek treatment for conditions in the future. This might mean that the impact of awareness and the costs of treating its consequences have been underestimated.

6.4 The Committee was advised that unintended awareness during surgery in patients who receive muscle relaxants is associated with more severe psychological harm than in patients who do not receive muscle relaxants.

6.5 The Committee noted that the risk of awareness during surgery in patients receiving inhaled anaesthesia can be reduced using structured anaesthesia protocols such as measuring end-tidal anaesthetic concentration with audible alarms and using MAC values, but the use of such protocols is not possible in patients receiving total intravenous anaesthesia. In patients who are more sensitive to anaesthetic and who are therefore at higher risk of receiving an excess of anaesthetic, such as older patients, the standard levels within such protocols may not be appropriate.

6.6 The Committee noted that unintended awareness during surgery could still occur with the use of depth of anaesthesia monitors or structured protocols for

measuring end-tidal anaesthetic concentration, but that the use of these interventions lowered the risk. The Committee considered that it is uncertain if the depth of anaesthesia monitors reduce the risk of consciousness without recall.

6.7 The Committee acknowledged that distinguishing between late psychological symptoms and post-traumatic stress disorder was difficult but concluded that the adverse impact on quality of life was the same. The Committee noted that the 2 groups had been separated in the cost-effectiveness analyses, and the costs associated with post-traumatic stress disorder were not applied to the group with late psychological symptoms. Therefore, the Committee concluded that the clinical benefits of monitoring could have been underestimated in the cost-effectiveness analyses.

6.8 The Committee considered there was uncertainty about the effects of excessively deep levels of anaesthesia. The Committee was advised that there was evidence suggesting an increase in morbidity and mortality associated with excessively deep anaesthesia (for example, an increase in the incidence of stroke or myocardial infarction). They also noted that there was weak evidence showing that excessively deep anaesthesia resulted in post-operative cognitive dysfunction. The Committee noted that these outcomes had not been included in the cost model, and that their absence meant that the clinical benefits of avoiding excessively deep levels of anaesthesia were likely to have been underestimated in the cost-effectiveness analyses.

6.9 Although the Committee considered that the clinical benefits associated with reducing adverse outcomes from anaesthesia were underestimated in the model, the Committee also discussed the uncertainty about the extent to which depth of anaesthesia monitoring could reduce these adverse effects and the consequent uncertainty about the cost savings. The Committee noted the possibility that the clinical benefits of monitoring may have been overestimated in the cost-effectiveness analyses.

6.10 The Committee noted that potential cost savings associated with reductions in operating theatre time and recovery time were not included in the model. The Committee considered that incorporating the cost savings associated with these outcomes might improve the cost effectiveness of the monitors, but the time

savings were too small to significantly benefit clinical practice.

6.11 The Committee considered the wide variation in price for the sensors for the 3 monitors (from under £1 to over £14). The Committee noted that there may be technical differences in the sensors, which could affect the accuracy of the monitors, but that there was no evidence of a substantial clinical difference when the sensors are used by anaesthetists well trained in depth of anaesthesia monitoring.

6.12 The Committee noted anecdotal evidence that the BIS monitor and sensors could be procured locally at a lower cost than that used in the model.

6.13 The Committee noted that despite many large studies, particularly of the BIS monitor, uncertainties remained about the probability of unintended awareness during surgery and the benefits of avoiding excessively deep levels of anaesthesia and, therefore, the extent to which depth of anaesthesia monitors could reduce adverse outcomes. The Committee considered the value of additional research studies before making its recommendations, but concluded that the size, complexity, cost and time requirements of such studies could unduly delay the uptake by the NHS of what is likely to be a beneficial technology.

6.14 The Committee concluded that additional research is desirable and should be undertaken by both the manufacturers and clinical researchers to provide additional information about the benefits and costs associated with the use of these technologies. In particular, information is needed about the clinical effectiveness of E-Entropy and Narcotrend-Compact M in reducing unintended awareness during surgery, as is further information about the effectiveness of all 3 monitors in reducing all adverse outcomes of general anaesthesia (including post-operative cognitive dysfunction). The Committee also wished to encourage further research into the clinical implications of accidental awareness during surgery, and the impact of the length and depth of anaesthesia on short- and long-term morbidity and mortality.

6.15 The Committee noted that the Royal College of Anaesthetists and the Association of Anaesthetists of Great Britain and Ireland have commissioned a National Audit Project (NAP5 – Accidental Awareness during General Anaesthesia [AAGA]) that

will collect data on all reported cases of accidental awareness during general anaesthesia during a 1-year time period. The results of this audit are expected to be published in 2014. The Committee felt that the data from this audit may be of some benefit when this guidance is reviewed. The Committee discussed the potential impact of this guidance on the validity of the audit and concluded that an adverse impact was unlikely.

6.16 The Committee noted that only literature written in the English language was included in the assessment, and therefore some studies, particularly on the Narcotrend-Compact M monitor, may not have been included in the evidence base. It was also noted that observational studies comparing the different technologies were not included in the evidence base.

6.17 The Committee noted that the modelling gave base-case ICERs for BIS that were above the usual levels accepted by NICE for the adoption of a technology. The Committee noted the considerable uncertainty in many of the parameters of the model and noted that the ICERs were very sensitive to small changes in the parameters. In addition, the Committee noted that the depth of anaesthesia monitors were relatively low-cost interventions, and it was likely that the clinical benefits of using the monitors were underestimated in the base case, particularly those benefits associated with avoiding excessively deep levels of anaesthesia. The Committee considered that the avoidance of uncommon but catastrophic events for patients was an important factor in accepting a technology with an ICER that appeared to be higher than usually acceptable in the base-case results.

6.18 The Committee noted that E-Entropy and Narcotrend-Compact M both had ICERs in the acceptable range, but that there was greater uncertainty about their clinical benefit than for the BIS monitor.

6.19 Notwithstanding the uncertainty in the evidence base, the Committee considered that depth of anaesthesia monitoring is most likely to be cost effective and of clinical benefit in patients receiving total intravenous anaesthesia and in patients considered at higher risk of unintended awareness or of excessively deep levels of general anaesthesia.

6.20 The Committee considered that anaesthetists using depth of anaesthesia monitors should ensure that they have appropriate experience with these

monitors and appreciate the potential pitfalls in their use in clinical practice. The Committee considered it important to note that the use of the monitors might require significant changes to clinical practice to achieve clinical benefit, and the skill and experience of the anaesthetist in using the depth of anaesthesia monitor are highly likely to influence the clinical effectiveness of the technique.

6.21 The Committee considered possible equality impacts and concluded that the recommendations would be unlikely to disadvantage any groups protected under equalities legislation.

7 Recommendations for further research

7.1 The Committee encourages further research as described in section 6.13 but has made no specific research recommendations. This is because, although there is uncertainty about many aspects of depth of anaesthesia monitoring (as described in section 6), the Committee considered that the current evidence base suggests depth of anaesthesia monitoring offers clinical benefits. Given the many complications in undertaking research in this area of anaesthesia, the Committee considered that the current uncertainty in the evidence base does not justify a potentially long delay in the uptake of what is likely to be a beneficial technology to the NHS and, particularly, to patients.

8 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for developing specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 7 into its guidance research recommendations database and highlight these recommendations to public research bodies.

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the Committee members who participated in this evaluation appears below.

Standing Committee members

Dr Trevor Cole
Consultant Clinical Geneticist, Birmingham Women's Hospital Foundation Trust

Dr Paul Collinson
Consultant Chemical Pathologist, St George's Hospital

Professor Ian Cree
Director of Efficacy and Mechanisms Programme, NIHR Evaluation, Trials and Studies Coordinating Centre, University of Southampton

Dr Erika Denton
National Clinical Director for Imaging, Department of Health

Dr Simon Fleming
Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Professor Elizabeth (Lisa) Hall
Professor of Analytical Biotechnology, Institute of Biotechnology, Department of Chemical Engineering and Biotechnology, University of Cambridge

Professor Chris Hyde
Professor of Public Health and Clinical Epidemiology, Peninsula College of Medicine and Dentistry

Professor Noor Kalsheker
Professor of Clinical Chemistry, Molecular Medical Sciences, University of Nottingham

Dr Mark Kroese
Consultant in Public Health Medicine, PHG Foundation and UK Genetic Testing Network

Professor Adrian Newland (Chair)
Consultant Haematologist, Barts and the London NHS Trust

Dr Richard Nicholas
Consultant Neurologist, Heatherwood and Wexham Park Hospital, Imperial Healthcare Trust

Ms Margaret Ogden
Lay member

Dr Diego Ossa
Global Head, Health Economic and Outcomes Research, Novartis Molecular Diagnostics

Mr Stuart Saw
Director of Finance and Procurement, Tower Hamlets Primary Care Trust

Professor Mark Sculpher
Professor of Health Economics, Centre for Health Economics, University of York

Dr Steve Thomas
Senior Lecturer and Consultant Radiologist, University of Sheffield

Mr Paul Weinberger
CEO, Diasolve Ltd, London

Mr Christopher Wiltsher
Lay member

Specialist Committee members

Dr John Andrzejowski
Consultant in Anaesthesia and Neurointensive Care, Royal Hallamshire Hospital, Sheffield

Professor Anthony Fisher
Consultant Clinical Scientist, Royal Liverpool and Broadgreen University Hospitals

Mr John Hitchman
Lay member

Dr David Smith
Consultant/Senior Lecturer in Cardiac Anaesthesia (A+B), Southampton General Hospital

Dr Andrew Smith
Consultant Anaesthetist, Royal Lancaster Infirmary

Professor Michael Wang
Professor of Clinical Psychology/Honorary Consultant Clinical Psychologist, University of Leicester

NICE project team

Each diagnostics assessment is assigned to a team consisting of a Technical Analyst (who acts as the topic lead), a Technical Adviser and a Project Manager.

Sarah Baggaley
Topic Lead

Hanan Bell
Technical Adviser

Jackson Lynn
Project Manager

10 Sources of evidence considered by the Committee

The diagnostics assessment report was prepared by the Southampton Health Technology Assessments Centre (SHTAC), University of Southampton.

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

Registered stakeholders

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

Manufacturers/sponsors:

- Covidien
- Draeger Medical UK Ltd
- GE Healthcare
- Masimo International
- Medical Device Management Ltd
- MT MonitorTechnik GmbH Co. KG

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

Update information

Minor updates since publication

December 2025: Diagnostics guidance 6 has been migrated to HealthTech guidance 292. The recommendations and accompanying content remain unchanged.

ISBN: 978-1-4731-7357-6