National Institute for Health and Clinical Excellence

Diagnostics consultation document

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

The National Institute for Health and Clinical Excellence (NICE) is producing guidance on using depth of anaesthesia monitors in the NHS in England. The Diagnostics Advisory Committee has considered the evidence submitted and the views of expert advisers.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the Committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report), which is available from http://guidance.nice.org.uk/DT/InDevelopment.

The Advisory Committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues
NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse impact on people with a particular disability or disabilities.

Note that this document is not NICE's final guidance on depth of anaesthesia monitors. The recommendations in section 1 may change after consultation.

After consultation the Committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the Committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the 'Diagnostics Assessment Programme process guide' (available at www.nice.org.uk/aboutnice/howwework/developingnnicediagnostictechnologiesguidance).

Key dates:

Closing date for comments: 25 June 2012

Second Diagnostics Advisory Committee meeting: 4 July 2012

1 Provisional recommendations

1.1 The use of the Bispectral Index (BIS) depth of anaesthesia monitoris recommended as an option for reducing adverse outcomes from anaesthesia in patients receiving total intravenous anaesthesia and also in patients who are at higher risk of complications from anaesthesia such as unintended awareness, cognitive dysfunction, and the adverse physiological effects of deep anaesthesia.

1.2 Although there is greater uncertainty of clinical benefit for the E-Entropy, and the 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 are therefore recommended as options for reducing adverse outcomes from anaesthesia in patients receiving total intravenous anaesthesia and also in patients who are at higher risk of complications from anaesthesia such as unintended awareness, cognitive dysfunction, and the adverse physiological effects of deep anaesthesia.

1.3 Anaesthetists considering using depth of anaesthesia monitors should ensure they are trained in their use in clinical practice.

2 The technologies

2.1 The Bispectral Index (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 to indicate the depth of anaesthesia in patients having surgery.

2.2 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 own anaesthesia systems.

3 Clinical need and practice

The problem addressed

3.1 Depth of anaesthesia monitors are designed to monitor the level of anaesthesia in patients receiving general anaesthetics and to aid the tailoring of anaesthetic dose to the individual patient. Measuring a patient's response to anaesthesia is important clinically because an inadequate level of anaesthesia can result in patient awareness during surgery which can cause post-traumatic stress disorder in some patients. Conversely, an excess of anaesthetic can result in prolonged recovery and an increased risk of postoperative complications, including cognitive dysfunction for some patients.

3.2 The aim of this evaluation is to determine the clinical and cost-effectiveness of three 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 which is achieved with drugs that provide haemodynamic stability and prevent awareness, pain, 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.

3.4 Individual variation in response to anaesthetics can occasionally lead to inadequate or excessively deep levels of anaesthesia. 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.

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 Side effects of excessively deep general anaesthesia 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. There is some evidence to suggest a link between longer term morbidity and mortality, and the length and depth of anaesthesia.

3.7 Groups of patients who are considered at higher risk of complications from general anaesthesia include older patients, those with a high body mass index (BMI), patients with airway problems, patients who have comorbidities and those undergoing certain types of surgery in which lower levels of anaesthetic are often used. Anaesthetic agents can affect the body's physiology, in particular, the cardiovascular system. As a result, anaesthetic levels are adjusted to prevent an adverse effect on the cardiovascular system of those patients who are already at a higher risk. Therefore, patients with comorbidities or patients undergoing certain types of surgery are at a higher risk of receiving inadequate levels of anaesthesia. In contrast, older patients and patients with a high BMI can be more sensitive to anaesthetic and are therefore at higher risk of receiving an excess of anaesthesia. .

The diagnostic and care pathways

3.8 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 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 pain-relieving drugs, 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 crying, 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 calculate the amount of oxygen in the blood, a device to measure the patient’s temperature, a device to monitor volatile agent concentration 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.

3.11 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 recovery room 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 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 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. The BIS module and sensors are only compatible with each other.

E-Entropy

4.2 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, response entropy (RE) and state entropy (SE).

4.3 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 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 40–60. RE and SE values near 40 indicate a low probability of consciousness.

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 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 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, crying and sweating) and measurement of one 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 (appendix A) considered evidence from a number of sources (appendix B), 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 three 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 postoperative recovery' provided a basis for the assessment of clinical effectiveness for 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 publication of 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 2–18 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 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.

5.3 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 confirmed or possible awareness during surgery with BIS monitoring and 30 cases with standard clinical monitoring. One trial monitoring inhaled 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 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 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 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. 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.

5.4 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 External Assessment Group to include the two further trials in patients at high risk of awareness during surgery. After the addition of these two 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 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.

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/min to –1.33 mg/kg per min but remained statistically significant.

5.7 Of the 11 trials, 5 reported time to extubation as a secondary outcome. All 5 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.

5.8 Five trials reported the time to discharge from the recovery room 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.

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 postoperative 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 postoperative nausea and vomiting.

5.11 The evidence on long-term cognitive dysfunction following general anaesthesia was limited to one study (reported in a conference abstract) of patients over 60 years of age. This study reported a reduction in postoperative 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. Two of these studies were conducted in children (aged 3–12 years). None of the trials were 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 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.

5.14 There was one case of awareness during surgery in the six trials that reported this outcome. This occurred in the standard clinical monitoring group. Sample sizes were small in all of the trials, so

rare events such as awareness during surgery may not 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 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 anaesthetic was found in a trial reporting the consumption of intravenous anaesthetic 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 with E-Entropy monitoring compared with standard clinical monitoring.

5.16 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 compared with standard clinical monitoring. Two of these trials reported statistical significance.

5.17 Two trials reported that the time to discharge from the operating room to the recovery room 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 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.

5.18 One trial conducted in patients receiving intravenous anaesthesia reported postoperative nausea and vomiting as a secondary outcome. There was no 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

5.19 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 in the study populations for awareness during surgery.

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

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

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

5.23 In one 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 1.4–6 minutes with Narcotrend-Compact M monitoring compared with standard clinical monitoring.

5.24 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

5.25 A systematic review of the evidence on cost effectiveness for the three 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.

5.26 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.

5.27 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 three technologies. No analyses were conducted to directly compare the technologies.

5.28 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 complications (such as post-operative nausea and vomiting) and long-term complications (such as post-traumatic stress disorder and post-operative cognitive dysfunction), and the risk of experiencing awareness during surgery.

5.29 The model was also used to estimate the costs associated with 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 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 complications 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 complications on quality of life was included in the model because by definition these are expected to be of short duration.

5.30 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 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.

5.31 For each monitor, four analyses were performed, two each for the population at general risk of complications from anaesthesia and the population at high risk of complications from anaesthesia. For each of the two populations, two analyses were performed, one for patients receiving total intravenous anaesthesia and one for a general mix of patients regardless of the type of anaesthesia.

5.32 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, £8.68 and £0.56 for BIS, E-Entropy and Narcotrend-Compact M respectively.

5.33 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 complications 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 complications 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 complications from anaesthesia receiving total intravenous anaesthesia

5.34 The base-case analysis for patients at high risk of complications from anaesthesia receiving total intravenous anaesthesia resulted in incremental cost-effectiveness ratios (ICERs) of £21,940, £14421 and £5681 per QALY gained for BIS, E-Entropy and Narcotrend-Compact M monitoring respectively, compared with standard clinical monitoring alone.

5.35 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.

5.36 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.

5.37 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.

5.38 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 complications from anaesthesia receiving total intravenous anaesthesia

5.39 The base-case analysis for patients at general risk of complications 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 dominates standard clinical monitoring in this population (that is, standard clinical monitoring was more expensive and less effective).

5.40 As in patients at high risk of complications 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 and was £44,491 per QALY gained when the probability was 0.001, compared with standard clinical monitoring alone; 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.

5.41 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

dominates standard clinical monitoring by generating improved outcomes at reduced costs.

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

5.42 The base-case analysis for patients at high risk of complications 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.

5.43 Sensitivity analyses showed that the ICERs for BIS, E-Entropy and Narcotrend-Compact M monitoring were all 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.

5.44 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.

5.45 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.

5.46 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 complications from anaesthesia receiving either intravenous or inhaled anaesthesia

5.47 The base-case analysis for patients at general risk of complications 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 dominates standard clinical monitoring in this population.

5.48 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.

5.49 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.

5.50 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.

5.51 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.

5.52 Scenario analyses were performed to investigate the impact of varying the assumed number of patients per monitor 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 three 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. These include 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 noted that awareness during surgery can be reduced using structured anaesthesia protocols such as measuring end tidal concentration of inhaled anaesthetic, but such protocols were not specifically evaluated in this evaluation.

6.5 The Committee acknowledged that distinguishing between late psychological symptoms and post-traumatic stress disorder was difficult but concluded that the impact on quality of life was the same. The Committee noted that the two 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.

6.6 The Committee considered there was uncertainty about the effects of excessively deep levels of anaesthesia. The Committee noted that there was weak evidence showing that excessively deep

anaesthesia resulted in post-operative cognitive dysfunction. However, 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). The Committee noted that these outcomes had not been included in the cost model but could have had a significant impact on the cost-effectiveness analyses because their absence meant that the clinical benefits of avoiding excessively deep levels of anaesthesia were likely underestimated.

6.7 Although the Committee considered that the clinical benefits associated with reducing complications 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.

6.8 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.

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

6.10 The Committee noted anecdotal evidence that the BIS monitor and sensors could be procured locally at a lower cost than that given in the NHS supply chain.

6.11 The Committee considered that there was uncertainty about many aspects of the use, benefits, and overall costs of these depth of anaesthesia monitors. It also noted that despite many large studies, particularly of the BIS monitor, these uncertainties remained. 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.

6.12 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 of these technologies. In particular, information about the clinical effectiveness of E-Entropy and Narcotrend-Compact M is needed as is information about the effectiveness of all three monitors in reducing all complications of anaesthesia (including post-operative cognitive dysfunction). The Committee would also encourage further research into the clinical implications of awareness during surgery, and the impact of deep anaesthesia on short- and long-term morbidity and mortality.

6.13 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.

6.14 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 considered that there was considerable uncertainty in many of the parameters of the model and 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 rare but catastrophic events for patients was a further consideration in accepting a technology with an uncertain ICER that appeared in the base case results to be higher than usually acceptable.

6.15 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 the BIS monitor.

6.16 Given 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 patients who are considered at higher risk of complications from general anaesthesia.

6.17 The Committee considered that appropriate training should be given to anaesthetists using depth of anaesthesia monitors because the monitors can 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 therefore likely to influence the clinical effectiveness of the technique.

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

7 Proposed recommendations for further research

7.1 The Committee encourages further research as described in section 6.12 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 suggested depth of anaesthesia monitoring offers clinical benefits. Given the many complications in doing research in this area of anaesthesia, the Committee considered that the uncertainty in the evidence base did 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 intends to develop tools, in association with relevant stakeholders, to help organisations put this guidance into practice.

9 Related NICE guidance

Published

- Caesarean section. NICE clinical guideline 132 (2011).
- Sedation in children and young people. NICE clinical guideline 112 (2010)
- Post-traumatic stress disorder (PTSD). NICE clinical guideline 26 (2005)

10 Review

NICE will update the literature search at least every 3 years to ensure that relevant new evidence is identified. NICE will contact product sponsors and

other stakeholders about issues that may affect the value of the diagnostic technology. NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, Appraisal Committee
June 2012

Appendix A: 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 O 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 Nick Summerton

General Practitioner, East Yorkshire

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, The 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 evaluation is assigned to a team consisting of one 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

Appendix B: 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 evaluation as registered stakeholders. They were invited to attend the scoping workshop and to comment on the diagnostics assessment report.

Manufacturers/sponsors:

The technologies under consideration

- 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