Depth of anaesthesia monitors - Bispectral Index, E-Entropy and Narcotrend-Compact M Diagnostics Consultation Document (DCD) – Comments

Comment no.	Consultee	Section no.	Comment	Response
1.	Consultee 1 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	I would urge the committee to rethink the draft guidance. Firstly, the evidence for use of BIS is, at best, equivocal. Recent evidence (eg. Avidan et al from the NEJM last year) suggests is it, at best, no better for preventing awareness than clinical monitoring in the high risk patient receiving volatile anaesthesia. ---------- Further to this, I would suggest that the timing of this guidance is poor, given that the 5th National Audit Project organised by the RCoA, which is currently recruiting, intends to explore the issue of awareness. As such, I would ask that the committee gives serious consideration to postponing the release of the final draft of this guidance until the results of NAP5 are known.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee did not consider the comparator used in the Avidan et al study (structured ETAC protocol with audible alarms) representative of current routine NHS practice. The Committee also noted that measuring ETAC is not possible in patients receiving total intravenous anaesthesia. ---------- The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.

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2.	Consultee 2 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	Without comparative studies it is difficult to conclude the different monitors are broadly equivalent. Most Council members felt the evidence base did not support the strength of recommendation. A minority felt that some form of cerebral function monitoring should be mandatory. Human error is the most common cause of awareness, which is less likely to be improved by the use of additional monitors.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee concluded that the three monitors are broadly equivalent.
3.	Consultee 3 Manufacturer	Section 1 Comment on Section 1: Provisional recommendations	The recommendations are a suitable basis for guidance to the NHS. Studies show that EEG monitoring helps to avoid stages of anaesthesia which are too light or unnecessarily deep. There are also studies that support the Committee`s conclusion that the Narcotrend-Compact M is broadly equivalent to the BIS.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.

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4.	Consultee 4 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	The Society for Intravenous Anaesthesia welcomes the recommendation that depth of anaesthesia monitoring be used as an option for reducing adverse outcomes from anaesthesia. However, we strongly disagree with the recommendation that this should apply specifically to patients receiving total intravenous anaesthesia. There is no good evidence that the risk of awareness resulting from inadequate anaesthetic dose or the risk of harm resulting from excessive anaesthetic dose differs between patients receiving intravenous or inhaled drugs to maintain anaesthesia. Indeed the NICE Technology Assessment Report uses identical baseline estimates of the risk of awareness during anaesthesia for patients receiving total intravenous anaesthesia and for patients receiving inhaled drugs to maintain anaesthesia (page 202). As the Provisional recommendations stand they give the reader the misleading impression that total intravenous anaesthesia is associated with a higher risk of awareness.	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance. The Committee did not consider patients receiving total intravenous anaesthesia 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.
5.	Consultee 5 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	Clinical evidence to date is too uncertain to make recommendations in favour of depth of anaesthesia monitors- see below	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.

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6.	Consultee 6 Manufacturer	Section 1 Comment on Section 1: Provisional recommendations	Recommend BIS monitoring for reducing adverse outcomes from inhaled and combination anaesthesia. The Cochrane review states that BIS monitoring reduces volatile anaesthetic usage by 0.17 MAC. No studies comparing BIS monitoring to standard clinical practice have shown otherwise. --- E-Entropy/Narcotrend are not equal to BIS in action to reduce adverse outcomes. NICE is uncertain of the clinical efficacy of E-Entropy/Narcotrend thus recommending them as options to BIS monitoring is not justified, may be misleading and may pose safety risks. Assuming all depth of anaesthesia monitors are the same contrasts with expert opinion. Dr. Sneyd (Editorial BJA 2004) notes "Individual monitors rely on different technologies" extrapolation of results between systems that monitor anaesthetic depth by completely different principles may be hard to justify." The efficacy of BIS monitoring to reduce awareness is established in trials appropriately powered to determine this patient safety impact the efficacy of E-Entropy/Narcotrend technologies is unknown. The Guidance Document should not recommend E-Entropy/Narcotrend monitors as options for reducing adverse outcomes from anaesthesia and project an efficacy impact without evidence.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered the cost-effectiveness analyses and concluded that the use of depth of anaesthesia monitoring was not cost-effective in patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia. --- The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee concluded that the three monitors are broadly equivalent.

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7.	Consultee 7 Manufacturer	Section 1 Comment on Section 1: Provisional recommendations	We would highlight to the Committee that the current wording in section 1 is open to mis-interpretation by the reader that the diagnostic assessment committee are recommending BIS as the first technology of choice, then E-Entropy and Narcotrend, when in fact all three technologies are being recommended. Ultimately it is the decision-maker who must review the evidence presented on each product to decide which is the most appropriate for their setting. As such we would suggest that section 1.1 be reworded to reflect that all of the depth of anaesthesia monitors have been recommended by the Diagnostic Assessment Committee for example:?The use of BIS, E- Entropy and Narcotrend depth of anaesthesia monitors are 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 comlications from anaesthesia such as unintended awareness, cognitive dysfunction and the adverse physiological effects of deep anaesthesia. We would also suggest that paragraph 1.2 is now redundant. The uncertainty around the data is fully explained within the DCD therefore the reader has sufficient informat	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance.

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8.	Consultee 8 Manufacturer	Section 1 Comment on Section 1: Provisional recommendations	1.1 We notice that use of the BIS monitor has only been recommended as an option for reducing adverse outcomes from anaesthesia in patients receiving total intravenous anaesthesia. We suggest that use of BIS monitoring also be recommended as an option for reducing adverse outcomes from inhaled and combination anaesthesia administration in addition to total intravenous anaesthesia administration. Inhaled anaesthetic cost was included as a model input parameter in the Diagnostics Assessment Report but appears to have been excluded from this interim analysis without explanation. The Cochrane review states that BIS monitoring reduces MAC volatile anaesthetic usage (desflurane, sevoflurane, isoflurane) by 0.17 minimal alveolar concentration equivalents (MAC) (noted in Section 5.6 of the Diagnostics Consultation Document). Since publication of the Cochrane review, no clinical studies that have compared BIS monitoring to standard clinical practice as defined in the NICE Diagnostics Consultation document have demonstrated otherwise.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered the cost-effectiveness analyses and concluded that the use of depth of anaesthesia monitoring was not cost-effective in patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia, but does recommend the use of these monitors for patients at higher risk of adverse outcomes.

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9.	Consultee 9 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	1.1. We do not agree that this statement is supported by the evidence, which is clearly too heterogenous to draw firm conclusions like this. There are four situations specified - total intravenous anaesthesia, unintended awareness, cognitive dysfunction and other (unspecified) adverse physiological effects of anaesthesia. Clearly, the evidence cannot be sufficiently strong to make a recommendation about all these four situations equally. Yet as written, that is the impression being created. ---------- Even if the recommendation were to stand, we already know from our NAP5 study that only a small minority of anaesthetists use any 'depth of anaesthesia' monitors (even in those hospitals that have acquired such monitoring); and that a tiny minority of hospitals have any guidelines on the prevention of accidental awareness. The combination of these two factors alone - as an example - make NICE's provisional recommendation 1.1 redundant, since it is impossible to adopt any technology in the absence of suitable contextual professional guidance. Yet, we are also surprised that no mention appears to be made of evidence that several common anaesthetic agents (including nitrous oxide and ketamine and others) do not seem to influence BIS readings and can cause problems of interpreting its results.	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance. ---------- Thank you for your comment. The Committee considered this comment and decided to change section 1.4 and section 6.20 of the guidance.
10.	Consultee 8 Manufacturer	Section 1 Comment on Section 1: Provisional	1.2 We challenge the conclusion and recommendation that E-Entropy and Narcotrend are equivalent to BIS in their action to reduce adverse outcomes in patients at higher risk of unintended awareness. The impact of the BIS monitoring	Thank you for your comment. The Committee considered this comment and decided not to change

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		recommendations	technology is established via the clinical studies and published evidence demonstrating the efficacy of incorporating BIS monitoring to reduce adverse outcomes from anaesthesia. However, to start with the acknowledged uncertainty regarding the clinical efficacy for the E-Entropy and Narcotrend monitors due to lack of published research, and then assume that these technologies have similar efficacy as the basis for recommending them as alternative options to BIS monitoring is not justified, potentially misleading, and may have unintended patient safety implications. The draft guidance document suggests and assumes that other depth of anesthesia monitoring technologies will have the same efficacy as BIS monitoring in reducing intraoperative awareness. We believe there is great risk in assuming all depth of anesthesia monitors are the same, and in fact, this assumption is in contrast to other expert opinion. Dr. J. R. Sneyd of the Peninsula Medical School in Plymouth, UK, in an editorial in the British Journal of Anaesthesia (Sneyd JR, 2004) stated:" Individual monitors rely on different technologies, such as polyspectral analysis, EEG entropy and AEP, and extrapolation of results between systems that monitor anaesthetic depth by completely different principles may be hard to justify." With this background we submit there is no justification for making the assumption that the other depth of anesthesia monitoring technologies will have the same impact as the BIS monitoring technology in reducing the incidence of awareness. The efficacy of the BIS monitoring technology to support a care strategy that reduces awareness has been assessed in large	the guidance. The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee concluded that the three monitors are broadly equivalent.

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			scale studies which specifically designed to around that patient safety outcome. Large scale studies examining the efficacy of either the E-Entropy or Narcotrend monitoring technologies have not been conducted. Hence, the impact of the E-Entropy and Narcotrend devices on reducing this adverse event remains unknown. The draft guidance should not project an efficacy impact when there is no imperative to justify such a projection. Additionally, we understand and respect that this guidance is concerned with cost-effectiveness as well as clinical outcomes. In the critical setting of the Operating Room for patients under anesthesia, however, patient safety is more critical than cost-effectiveness. Key safety endpoints for depth of anesthesia monitors, thus rigorous clinical trials, are critical. We believe there is great risk in a guidance that implies that efficacy of depth of consciousness monitoring does exist when in fact for the E-Entropy and Narcotrend monitors, it has not been established, potentially putting patients at risk. We believe the Committee should reconsider its recommendation that the E-Entropy and Narcotrend monitors be considered an option for reducing adverse outcomes from anesthesia administration, or at minimum make it clear to clinicians that efficacy and safety data has been extrapolated from large scale BIS studies specifically designed and powered to detect adverse events.	

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11.	Consultee 9 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	1.2. The first sentence of this paragraph is at odds with the second sentence. If there is greater uncertainty about these monitors, how is it they can be considered broadly equivalent? And conversely why are they recommended in this way - exactly as for BIS - if there is greater uncertainty? In other words, it seems here that the degree of uncertainty is irrelevant to the recommendation. This is an unusual stance to take since, in normal scientific thinking, conclusions should be guided by the degree of uncertainty. That which has greater uncertainty should logically lead to a different conclusion from that which as more certainty.	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance.
12.	Consultee 8 Manufacturer	Section 1 Comment on Section 1: Provisional recommendations	1.3 We suggest recommending that in addition to training, that the Guidance document should emphasize that depth of anaesthesia monitoring should not be used in isolation or as the sole monitoring parameter to guide patient care. The guidance document should state that clinicians should augment routine clinical observation and standard clinical monitoring with depth of anaesthesia monitoring to fully assess a patient's depth of anesthesia. A clinical integration framework is an important step to ensure optimal use of the patient monitoring information. Training should emphasize safe and effective use of a particular technology including a thorough review of the operating characteristics and artifact issues related to a particular technology. The BIS monitoring technology has the most comprehensive and published clinical experience providing a solid foundation for clinical integration as well as operating characteristics and artifact situations. Covidien provides 1:1 training in theatre and runs Peer lead teaching/lecture programmes for all users.	Thank you for your comment. The Committee considered this comment and decided to change sections 1.4, 2.1 and section 6.20 of the guidance.

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13.	Consultee 9 NHS Professional	Section 1 Comment on Section 1: Provisional recommendations	1.3. We do not understand this recommendation. 'Training' in the use of the monitor requires more than just being told how to use it by a manufacturer. Training requires that the anaesthetist is able to apply the measurement in the context of a wider course of professional training. This statement therefore has very wide implications (which are unfortunately not addressed in this report) for the specialty of anaesthetics as a whole. At an even more fundamental level any training must also rely upon a model of consciousness. This is akin to needing a model for the cardiovascular system before being able to apply any monitoring technology to it. Since no such model exists for consciousness, then at best, recommendation 1.3 would seem premature. We therefore suggest re-writing 1.3 to read: "Before 'depth of anaesthesia' monitoring can be adopted, scientific and professional guidance and training will be needed in order to interpret the monitor outputs in the context of a model for unconsciousness during anaesthesia."	Thank you for your comment. The Committee considered this comment and decided to change section 1.4 and section 6.20 of the guidance.
14.	Consultee 2 NHS Professional	Section 2 Comment on Section 2: The technologies	Many Council members questioned the assumption that EEG-monitors indicate the depth of anaesthesia. They are another means of assessment and indicate a probability of awareness rather than an absolute state. Aminority of Council members strongly supported the use of cerebral function monitoring during anaesthesia and intensive care.	Thank you for your comment. The Committee considered this comment and decided to change section 2.1 and section 3.1 of the guidance.

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15.	Consultee 4 NHS Professional	Section 2 Comment on Section 2: The technologies	The Technology Assessment report concluded that when BIS monitoring is compared to standard clinical monitoring, the odds ratio for the reduction in the risk of awareness from BIS monitoring in studies of total intravenous anaesthesia or mixed anaesthesia (intravenous in some patients, inhalational in some patients) is similar but that the benefits are less in studies of inhalational anaesthesia alone. This conclusion is entirely driven by the inclusion of 2 studies by Avidan (refs 27 and 44). However, the care in the non-BIS group in these studies of inhalational anaesthesia cannot remotely be described as standard clinical care. It involved calculating MAC and setting an audible alarm to go off whenever the end tidal anaesthetic gas concentration fell outside the range 0.7 ? 1.3 MAC. Such a protocol is very rarely followed in clinical practice in the UK so these studies cannot be regarded as being studies of BIS monitoring against standard care and should not be used to conclude that BIS monitoring is of less benefit in patients receiving inhalational anaesthesia.	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in the Avidan studies and concluded that this structured protocol was not representative of current routine NHS practice (standard clinical monitoring). The Committee considered the cost-effectiveness analyses and concluded that the use of depth of anaesthesia monitoring was not cost-effective in patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia, but does recommend the use of these monitors for patients at higher risk of adverse outcomes.

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16.	Consultee 10 NHS Professional	Section 2 Comment on Section 2: The technologies	We write in response to the above consultation, on behalf of the steering panel of the 5th National Audit Project of the Royal College of Anaesthetists and Association of Anaesthetists of Great Britain and Ireland (NAP5). Separate responses may also be submitted by the Association and College themselves. The core of NAP5 is an in-depth, year-long, service evaluation throughout the UK and Ireland to identify all new reports of accidental awareness during general anaesthesia (AAGA). The NAP5 data collection period started on 1st June 2012 and will run until 31st May 2013. NAP5 will provide unique new information about AAGA which will be directly relevant to the analyses performed by NICE regarding depth of anaesthesia monitors. This letter is to inform you of this major project and to explain our concerns that the publication of the NICE report and recommendations before completion of NAP5 would create the risk that NICE and NAP5 might produce different and conflicting recommendations. NAP5 will yield important information about numerous aspects of AAGA - notably the incidence of patient reports of AAGA. Your consultation document makes it clear that the cost-benefit analysis of depth of anaesthesia monitoring is, in many parts, highly sensitive to the incidence of such events. It would therefore potentially enhance the quality of the final NICE report and recommendations if it were possible to find a mechanism by which the findings of NAP5 were to be included.	Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.

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			NAP5 has a number of other work-streams which may also add value to the NICE report. For example, the role of depth of anaesthesia monitoring in cases of AAGA will be identified in a larger cohort of cases of AAGA than has ever been examined before. NAP5 has already established that only a small minority of anaesthetists use any depth of anaesthesia monitors (even in those hospitals that possess them) and that a tiny minority of hospitals have any guidelines on the prevention of AAGA. Such guidelines are essential if any monitoring is to be adopted meaningfully. Additionally, our early results suggest that a large proportion of incidents of AAGA occur after induction of anaesthesia but before surgery has commenced: this has important implications for the timing and interpretation of any monitoring. NAP5 will probably be the largest examination of AAGA ever conducted and will certainly be largest such examination ever conducted in the UK. We would like to highlight the possibility that NAP5 might lead to quite different conclusions and recommendations than those currently proposed by NICE which are (as stated in the report) based on heterogeneous studies performed outside the UK. The publication of two high level reports, soon after each other, with differing recommendations would clearly be undesirable. It is also important to appreciate that publication of the NICE guidance might also have an impact on NAP5 which we hope will examine a reasonably stable ?anaesthesia setting? such that anaesthetists? practices do not substantially change	

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			during the period of the project. Publication of the NICE report would potentially lead to changes in practice as a result of implementation of the recommendations. This would likely evolve over a period of months in an uncertain manner in terms of speed and penetration making it very difficult, if not impossible, to track the effects of this on the results of NAP5. NAP5, in addition to the two lead partner organisations, is joined by many anaesthesia sub-specialty organisations and includes collaborations practice. We have a robust network of almost 400 project Local Co-ordinators established, covering every NHS hospital in the UK and the Republic of Ireland. NAP5 processes are approved by NIGB (National Information Governance Board for England & Wales), PAGs (Patient Advisory Groups for Scotland & Northern Ireland), NRES (National Research Ethics Service) and equivalent bodies in the Republic of Ireland. The project has received approval from HQIP (Healthcare Quality Improvement Partnership) for inclusion on its directory of clinical registers and databases. Finally, the project has been endorsed by all four Chief Medical Officers representing the nations of the UK. More information is available on our website http://www.nationalauditprojects.org.uk/NAP5_home. We would like to work with NICE in an effort to ensure both our projects can achieve the best outcomes for patients and clinicians and would be happy to share our early outcomes with you in order to achieve that aim. We believe that ideally	

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			a modest postponement of the publication date of the NICE report might provide an opportunity to supplement this with important new data and thus make its recommendations more robust and durable. We would welcome the opportunity to discuss this.	
17.	Consultee 6 Manufacturer	Section 2 Comment on Section 2: The technologies	The Other Manufacturers? list needs to be expanded fully for the BIS monitoring technology. Mennen Medical, Philips, Drager, Spacelabs, Datascope, Nihon Kohden, Dixtal, Mindray and GE have all licensed the BIS technology from Covidien and produce BIS modules that are compatible with their own anaesthesia and patient multi-parameter monitoring systems. Between both standalone monitors as well as integrated systems through these other manufacturers, BIS technology is effectively available in 100% of UK Operating Theatres and Intensive Care Units.	Thank you for your comment. The Committee considered this comment and decided to change section 2.2 of the guidance.
18.	Consultee 9 NHS Professional	Section 2 Comment on Section 2: The technologies	2.1 The phrase to which we object (in this paragraph and all others) is the notion of 'depth' of anaesthesia. There is absolutely no evidence in the literature (scientific or clinical) that 'anaesthesia' has 'depth'. This is an unfortunate colloquialism which is being discouraged and phased out by those who study the science and it would therefore be more consistent to use a different terminology, or acknowledge that the term is used only by manufacturers. We would prefer the term ‘monitor of conscious state’.	Thank you for your comment. The Committee considered this comment and decided to change section 2.1 and section 3.1 of the guidance.

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19.	Consultee 8 Manufacturer	Section 2 Comment on Section 2: The technologies	2.2 The “Other Manufacturers” list needs to be expanded fully for the BIS monitoring technology. Mennen Medical, Philips, Drager, Spacelabs, Datascope, Nihon Kohden, Dixtal, Mindray and GE have all licensed the BIS technology from Covidien and produce BIS modules that are compatible with their own anaesthesia and patient multi-parameter monitoring systems. Between both standalone monitors as well as integrated systems through these other manufacturers, BIS technology is effectively available in 100% of UK Operating Theatres and Intensive Care Units.	Thank you for your comment. The Committee considered this comment and decided to change section 2.2 of the guidance.
20.	Consultee 2 NHS Professional	Section 3 Comment on Section 3: Clinical need and practice	There is increasing evidence that anaesthesia may not be totally reversible, and pharmacogenteics may contribute as much to this as depth of anaesthesia. The use of crying is an emotive description of a patients response in a document which otherwise is highly technical lacrimation would have been more objective.	Thank you for your comment. The Committee considered this comment and decided to change section 3.10 of the guidance.

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21.	Consultee 4 NHS Professional	Section 3 Comment on Section 3: Clinical need and practice	Awareness during anaesthesia that is associated with significant psychological distress, late psychological symptoms or post-traumatic stress disorder occurs almost exclusively when a muscle relaxant drug has been given. (This conclusion is based on a review of the published literature and personal communication from Professor M Wang.) Therefore, the key factor in determining whether BIS or other depth of anaesthesia monitoring is likely to be of benefit is not the route by which the general anaesthetic drugs are administered but rather whether or not a muscle relaxant is given. We therefore strongly recommend that the Provisional Recommendation 1.1 be amended to read: The use of the Bispectral Index (BIS) depth of anaesthesia monitor is recommended as an option for reducing adverse outcomes from anaesthesia in patients receiving a muscle relaxant during general anaesthesia, particularly 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.?	Thank you for your comment. The Committee considered this comment and decided to add explanatory text to section 1 and add section 6.4 to the guidance.

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22.	Consultee 6 Manufacturer	Section 3 Comment on Section 3: Clinical need and practice	"Standard clinical monitoring," the comparator for assessing depth of anesthesia, must be accurately portrayed. BIS monitoring for depth of anesthesia to avoid intraoperative awareness was studied in 3 large trials involving "standard clinical monitoring" (Myles et al 2004 Avidan et al 2008, 2011). However the Avidan studies used a protocol targeting volatile anesthetic administration and defined enhancement to "standard clinical monitoring" of end-tidal anesthetic administration. The guidance document must state that 2 studies involving a protocol administration of volatile anesthesia in combination with alarm alerts around a minimum concentration of volatile anesthesia detected through ETAC monitoring have shown equivalent efficacy in yielding a low incidence of intraoperative awareness compared to anesthesia care with BIS monitoring. There is no evidence that "standard clinical monitoring" as recognized and used by anesthesia professionals impacts the incidence of intraoperative awareness. It is inaccurate and a potential safety risk to imply that "standard clinical monitoring" would have the same results seen in the Avidan studies. BIS monitoring-guided anesthesia or targeted volatile anesthetic administration and enhanced end-tidal gas monitoring are alternative strategies to "standard clinical monitoring" to reduce the incidence of intraoperative awareness.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in the Avidan studies and concluded that this structured protocol was not representative of current routine NHS practice (standard clinical monitoring).

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23.	Consultee 11 NHS Professional	Section 3 Comment on Section 3: Clinical need and practice	The association between low BIS values and poor outcomes in high risk patients is not necessarily caused by excessive anaesthesia - there are other potential mechanisms. See e letter on Anaesthesia Correspondence website at http://www.respond2articles.com/ANA/forums/post/1100.aspx and references. This is important because possible interventions to raise a low BIS value,which may or may not improve outcomes, include such things as raising blood pressure, not just reducing the depth of anaesthesia	Thank you for your comment. The Committee considered this comment and decided to change section 1.4 and section 6.20 of the guidance.
24.	Consultee 9 NHS Professional	Section 3 Comment on Section 3: Clinical need and practice	3.4 The implication of the opening two sentences would be that excessive anaesthesia causes vomiting, headaches and dizziness. We are not aware of any evidence that supports this. --- It is also suggested here that the incidence of accidental awareness is known, and of an order which is very high (1 to 2 in 1000). But this is exactly what NAP5 will ascertain - for example, the figures quoted are not recognised by most anaesthetists to be the case.	Thank you for your comment. The Committee considered this comment and decided to change section 3.4 of the guidance. --- Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.

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25.	Consultee 9 NHS Professional	Section 3 Comment on Section 3: Clinical need and practice	3.5 It is stated here as if it were fact that these types of surgery/patient are associated with greater incidence of awareness, but this is not known. NAP5 will help establish if this is the case. The section of the paragraph starting "The use of muscle relaxants.." is, however, acceptable.	Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance.

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26.	Consultee 8 Manufacturer	Section 3 Comment on Section 3: Clinical need and practice	3.9 In our experience the majority of these Anaesthetic rooms do not have wired anaesthesia monitoring systems; therefore, a standalone monitor is required during anaesthesia induction to ensure that the drug titration is adequate. This is particularly important because Anaesthetic rooms are the location of airway management following the induction of anaesthesia. Unanticipated difficult intubation is a recognized risk factor for unintended awareness. BIS monitoring systems provide enhanced flexibility and cost effectiveness because they allow the clinician to use a single sensor per patient and utilize the same monitoring technology from different sources. For example the BIS sensor can be used during induction and airway management with a standalone monitoring system in the anaesthetic room, and then used with an integrated BIS system from other manufacturers in the Operating Theatre. Because E-Entropy systems are only available as integrated modular systems and Narcotrend systems are only available as standalone monitors, they do not provide the same flexibility to facilitate comprehensive access between both Anaesthetic rooms and Operating Theatres. Thus, the Guidance Document could consider the potential impact of technology access in Anaesthetic Rooms, Operating Theatres and ICUs – a hospital-wide system that enables efficiencies for training (and its associated time and cost).	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. Your comment has been passed to the NICE guidance implementation team.
27.	Consultee 8 Manufacturer	Section 3 Comment on Section 3: Clinical need and	3.10 It is appropriate to introduce the depth of consciousness monitoring procedure in this section. End-tidal anaesthesia agent concentration (ETAC) is a method of monitoring and measuring volatile anesthetic concentration. . ETAC informs	Thank you for your comment. The Committee considered this comment and decided to add sections

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		practice	the clinician of the inhaled anaesthetic concentration in exhaled breath. The clinician can utilize that concentration measure in the determination of the depth of anesthesia. Due to pharmacodynamics considerations; a given anaesthetic concentration can affect different patients in different ways. BIS is both an enhancement and alternative to end-tidal gas monitoring. The value shown on the BIS monitor reflects the individual patient-derived anesthetic effect based upon analysis of the patient's cortical EEG, indicating the EEG effect of a given anaesthetic state (intravenous, inhaled or a combination) on the effect site (the brain). The draft guidance refers to “standard clinical monitoring” as the comparator for assessing depth of anesthesia and intraoperative awareness. It is imperative that the Guidance Document accurately portray "standard clinical monitoring" as opposed to a specific protocol utilized in a clinical investigation. It is misleading to anesthesia professionals, and a patient safety issue, to utilize two clinical investigations as the evidence of a "standard clinical monitoring" comparator. BIS monitoring for depth of anesthesia as a specific intervention to avoid intraoperative awareness has been assessed in three large scale studies involving "standard clinical monitoring" (Myles et al, 2004, Avidan et al, 2008; Avidan et al, 2011). It is extremely important to note that the latter two studies utilized a specific protocol targeting volatile anesthetic administration as well as defined enhancement to "standard clinical monitoring" of end-tidal anesthetic administration. (Avidan et al, 2008; Avidan et al, 2011). It is essential that the guidance	6.5 and 6.6 to the guidance.

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			document clearly delineate and expressly state that 2 studies involving a protocol administration of volatile anesthesia in combination with alarm alerts around a minimum concentration of volatile anesthesia detected through end-tidal anesthetic concentration monitoring have demonstrated equivalent efficacy in yielding a low incidence of intraoperative awareness compared to anesthesia care involving BIS monitoring. There is no evidence that "standard clinical monitoring" – as recognized and utilized by current anesthesia professionals is able to have any impact on the incidence of intraoperative awareness. It is factually inaccurate, inappropriate and misleading to imply that the "standard clinical monitoring" would result in the same benefits as observed in the two Avidan clinical investigations. It would be more accurate to state that the addition of BIS monitoring and BIS-guided anesthesia or targeted volatile anesthetic administration and enhanced end-tidal gas monitoring are alternative strategies to current "standard clinical monitoring" to reduce the incidence of intraoperative awareness.	
28.	Consultee 2 NHS Professional	Section 4 Comment on Section 4: The diagnostics tests	See previous comment on crying. Council members were concerned that UK practice, particularly the use of end-tidal anaesthetic agent monitoring was not adequately reflected in the evidence.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance.

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29.	Consultee 4 NHS Professional	Section 4 Comment on Section 4: The diagnostics tests	And that the Provisional Recommendation 1.2 be amended to read: 'these are therefore recommended as options for reducing adverse outcomes from anaesthesia in patients receiving a muscle relaxant during general anaesthesia, particularly 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.'	Thank you for your comment. The Committee considered this comment and decided to change section 1 of the guidance.
30.	Consultee 5 NHS Professional	Section 4 Comment on Section 4: The diagnostics tests	Diagnosis of awareness can be made using different tools (e.g. post op interviews. There is a large discrepency between the awareness incidences both between studies and within studies(multi-centre studies), a difference made worse by the discrepencies in rates using different interview techniques. The total variation of awareness in all studies is greater than any treatment effect from using a depth of anaesthesia monitor: So, any monitor is unlikely to alter awareness by more than any effect seen by study methodology effects.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The structured modified Brice interview was used as the method for detecting awareness with recall in this evaluation. The Committee considered the heterogeneity and uncertainty within and between studies, and concluded that it arose mainly from the individual response to anaesthesia, case mix and variation in administering anaesthesia.

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31.	Consultee 6 Manufacturer	Section 4 Comment on Section 4: The diagnostics tests	Add BIS is compatible with anesthesia monitors manufactured by Mennen Medical, Philips, Drager, Spacelabs, Datascope, Nihon Kohden, Dixtal, Mindray and GE. The BIS/BISx compatibility with these anesthesia systems means 100% of UK operating theatres are compatible with the BIS sensor. ---------- Use of end-tidal alarms is not standard practice and is rarely used. The standard clinical monitoring comparator described in the Guidance includes end-tidal anesthetic gas monitoring however, use of end-tidal alarms to assess age-adjusted MAC values is not routinely used or standard practice. Unfortunately, the DAR and the Guidance repeatedly interpret ETAC with alarms to be standard clinical practice. The reports? interpretations of those studies comparing BIS to low-ETAC alarm protocols must be reevaluated since both techniques are not employed in standard clinical practice. This is factually inaccurate, inappropriate and misleading: while "standard clinical monitoring" does typically measure end-tidal gas monitoring, this monitoring does not routinely display the age-adjusted MAC value of the measured gas concentration, does not include audible alarms, and "standard clinical monitoring" does not included a targeted dose range for volatile anesthetic administration. The "comparator" is inaccurate, misleading, and is a patient safety issue due to lack of clarity.	Thank you for your comment. The Committee considered this comment and decided to change section 2.2 of the guidance. ---------- Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in the Avidan studies and concluded this structured protocol was not representative of current routine NHS practice (standard clinical monitoring).

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32.	Consultee 12 Private Sector Professional	Section 4 Comment on Section 4: The diagnostics tests	ETCO2 shown to be superior. As the evidence suggest this, use ETCO2 instead.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
33.	Consultee 8 Manufacturer	Section 4 Comment on Section 4: The diagnostics tests	4.1 Please add new section 4.1A, to state: BIS is a plug-in module that is compatible with anaesthesia monitors manufactured by Mennen Medical, Philips, Drager, Spacelabs, Datascope, Nihon Kohden, Dixtal, Mindray and GE. Brain EEG activity is acquired via a disposable sensor with 4 electrodes that adheres to the patient's forehead and connects to a BIS module via a patient interface cable. The patient-monitor cable includes a BISx component that receives, filters, and processes patient EEG signals which are then transmitted to the module. Because of the BIS/BISx compatibility with multiple manufacturer anaesthesia systems, the manufacturer estimates that 100% of all UK operating theatres would be compatible with the BIS sensor. Depending on the anesthesia monitor used, BIS use may or may not require investment in new monitoring equipment.	Thank you for your comment. The Committee considered this comment and decided to change section 4.1 of the guidance.

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34.	Consultee 9 NHS Professional		4.1-4.5 It is correctly stated that for these monitors, the output values reflect a certain "probability of recall". We agree with this sentiment, but what is then essential to know is what that probability actually is. In other words, if anaesthetists are to adopt this technology as is being advised, then it is essential they are clearly told that, say, a BIS value of x means 10% chance of recall, a value y means 20% chance and so on. It is notable that this essential information is absent from the NICE document and recommendations. Furthermore, given that NICE already accepts that the output from these monitors reflects a certain probability of recall, the appropriate guidance for NICE to provide is the probability of recall that is judged acceptable.	Thank you for your comment. The Committee considered this comment and decided to change sections 1, 2.1 and section 6.20 of the guidance.
35.	Consultee 8 Manufacturer	Section 4 Comment on Section 4: The diagnostics tests	4.6 We note and agree with the inclusion of end-tidal anaesthetic gas monitoring as a component of standard clinical monitoring; however, it should be noted that use of end-tidal alarms is not routinely used and is clearly not standard practice. On careful review of the standard clinical monitoring comparator described in the Diagnostics Consultation Document (section 4.6) we note that end-tidal anaesthetic gas concentration (ETAC, for inhaled anaesthesia) is considered a component of standard clinical monitoring; however, it should be noted that use of end-tidal alarms to assess age-adjusted MAC values is not routinely used or standard practice. Unfortunately, the DAR and the Diagnostics Consultation Document repeatedly interpret ETAC with alarms to be standard clinical practice. Consideration should be given to the re-evaluation of the reports' interpretations of those studies comparing BIS to	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in the Avidan studies and concluded this structured protocol was not representative of current routine NHS practice (standard clinical monitoring).

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			low-ETAC alarm protocols since both techniques are not employed in standard clinical practice. The draft guidance refers to “standard clinical monitoring” as the comparator for assessing depth of anesthesia and intraoperative awareness. The draft guidance implies that anesthesia concentration monitoring with alarms that alert anesthesiologists to maintain a minimum concentration or threshold of anesthesia is, in fact, “standard clinical monitoring" and assumes that the volatile anesthetic concentration targets used in two clinical investigations is the standard approach to anesthesia care. This is factually inaccurate, inappropriate and misleading: while "standard clinical monitoring" does typically end-tidal gas monitoring, this monitoring does not routinely display the age-adjusted MAC value of the measured gas concentration, does not include audible alarms, and the "standard clinically monitoring" does not included a targeted dose range for volatile anesthetic administration. Thus the "comparator" is inaccurate, misleading, and is a patient safety issue due to lack of clarity. The Guidance document would be greatly enhanced and more factually correct to consider BIS-guided anesthesia care and ETAC-guided anesthesia care (as described in the various studies) as alternatives to the actual "standard clinical monitoring" approaches to depth of anesthesia monitoring to avoid intraoperative awareness.	

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36.	Consultee 9 NHS Professional	Section 4 Comment on Section 4: The diagnostics tests	4.6 It is correctly stated here that end-tidal anaesthetic gas monitoring is used as a comparator. However, this is at odds with the statement 6.4 later that "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". Only one of these statements can be true – either that in 4.6 or that in 6.4.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee noted that the comparator included end-tidal gas monitoring but did not include the use of end-tidal gas monitoring within a structured protocol with audible alarms.

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37.	Consultee 2 NHS Professional	Section 5 Comment on section 5: Outcomes	The majority of Council did not believe that the admitted uncertainty about the use, costs, and benefits of such monitors justified the conclusions. There was concern about the wide variation in the ICERs achieved by the economic model, which was not published.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered that the heterogeneity and uncertainty in the studies and that ICERs arose mainly from the individual response to anaesthesia, the case mix and the variation in administering anaesthesia in clinical practice. The Committee considered that depth of anaesthesia monitoring offered clinical benefits associated with reducing the risk of adverse outcomes fom anaesthesia and noted that some adverse outcomes could have severe consequences for a patient's quality of life. All registered stakeholders are able to request a copy of the economic model during consultation.

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38.	Consultee 4 NHS Professional	Section 5 Comment on section 5: Outcomes	In paragraph 5.6 the unit specified for the reduction in propofol consumption is incorrect. It should be mg/kg/h not mg/kg/min.	Thank you for your comment. The Committee considered this comment and decided to change section 5.6 of the guidance.
39.	Consultee 5 NHS Professional	Section 5 Comment on section 5: Outcomes	Most awareness with recall involves auditory symptoms. This could be cheaply and easily reduced by universal use of earplugs, rather than recommending significantly expensive monitors which will not reduce the incidence to zero. The suggestion to ude depth of anaesthesia monitors is perhaps an example of the Pareto principle in action- acheiving the last small improvement takes an inordinate amount of effort.In this case, in an era of budget restraints, every pound spent on BIS etc is a pound less to spend on other, better proven technologies	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
40.	Consultee 6 Manufacturer	Section 5 Comment on section 5: Outcomes	Accurately portray 'standard clinical monitoring' as previously described.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in the Avidan studies and concluded this structured protocol was not representative of current routine NHS practice(standard clinical

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				monitoring).
			----------	----------
			Correct the statement 'these three trials were not designed to detect awareness during surgery.' The first two trials cited (Avidan 2011, Zhang 2011) were designed to detect awareness as a primary endpoint.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The three trials referred to in section 5.3 which were not designed to detect awareness did not include the studies by Avidan or Zhang studies. The trials referred to were by Kamal et al; Liao et al and Ellerkamn et al.
			----------	----------
			The extension of the efficacy of BIS monitoring to E-Entropy/Narcotrend is not justified.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee

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				concluded that the three monitors are broadly equivalent.
			----------	----------
			CE models should include savings associated with reduced post operative time in the operation room and PACU. According to the YHEC CE model (submitted), that would lead to an average saving of £45 per operation. The YHEC CE model assumed that at least 18% of those who experience AR will also experience anxiety and other psychological symptoms requiring medical treatment or behavioral therapy at an average cost of £925 per case.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered incorporating the cost savings associated with reductions in operating theatre time and recovery time might improve the cost effectiveness of the monitors, but the time savings were too small to significantly benefit clinical practice.
			----------	----------
			Include cost of GE module in the cost analysis.	The cost of the GE module was included in the cost-effectiveness analyses.
			----------	----------
			ICER values found by NICE may be overestimated due to underestimation of BIS-associated savings. See YHEC model for the significant net savings and loss aversions demonstrated. Include post operative nausea and vomiting	The Committee noted that there was uncertainty about the effects of excessively deep levels of anaesthesia

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			(PONV) as a model input parameter. Results of the YHEC CE model proved robust to sensitivity analyses. When all outcomes except stroke and death were considered BIS was cost-saving in 60% of cases with a max cost of £70 per operation and a max ICER of £3406, significantly lower than the ICER values identified by the NICE External Assessment Group.	and that avoidance of these effects were likely to have been underestimated in the cost-effectiveness analyses. The Committee decided to change section 6.8 of the guidance.
41.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.1 We notice that post operative nausea and vomiting, which was included as a model input parameter in the Diagnostics Assessment Report, appears to be absent from the Diagnostics Consultation Document. Although PONV was not an outcome measure of the Cochrane BIS review, an earlier meta-analysis (Liu, 2004) found evidence that BIS-guided anaesthesia care in ambulatory surgery reduced the incidence and costs associated with PONV. The York Health Economics Consortium (YHEC) model found that reduction in PONV was a determinant of savings associated with the use of BIS in an OR. We suggest that post operative nausea and vomiting, because it impacts both cost of hospitalization as well as patient satisfaction, be included as a model input parameter.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. No robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting were identified so scenario analyses were performed using data from the meta-analysis by Liu, 2004. The scenario analyses showed that the incremental costs for BIS monitoring were reduced but the ICERs remained largely unchanged for all of the population groups.

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42.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.2 We note the statement that the External Assessment Group identified 11 randomized 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". As previously stated, the Draft Guidance document is making a fundamental factual error by including clinical investigations that utilized a structured protocol around volatile anesthetic administration and end-tidal gas monitoring as evidence for a comparator of "standard clinical monitoring".	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of a structured ETAC protocol with audible alarms in some studies and concluded this structured protocol was not representative of current routine NHS practice (standard clinical monitoring).

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43.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.3 We note the first study cited indicated that fewer awareness cases occur during "standard clinical monitoring" compared to the BIS-monitored group. First, we must point out that the statistical analysis of results of this study indicate that there is no significant difference in the treatment effect of the protocols – the finding of "fewer awareness" cases is simply a line from the results table and is not a meaningful or statistically significant finding. ---------- Second, on careful review of the standard clinical monitoring comparator described in the Diagnostics Consultation Document (section 4.6) we note that end-tidal anaesthetic gas concentration (ETAC, for inhaled anaesthesia) is considered a component of standard clinical monitoring; however, it should be noted that use of end-tidal alarms to assess age-adjusted MAC values is not routinely used or considered standard practice at the current time. Unfortunately, the DAR and the Diagnostics Consultation Document interpret ETAC with alarms to be standard clinical practice. Consideration should be given to the re-evaluation of the reports' interpretations of those studies comparing BIS to low-ETAC alarm protocols since both techniques are not employed in standard clinical practice.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The difference in cases of awareness between the BIS-monitored group and standard clinical monitoring group is stated as not statistically significant in section 5.3 of the guidance document. ---------- Thank you for your comment. The Committee considered the use of structured ETAC protocols with audible alarms and concluded these structured protocols were not representative of current routine NHS practice (standard clinical monitoring). Standard clinical monitoring included ETAC without audible alarms.

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44.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.3 In this section it is stated that "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." With respect to the first two trials cited (Avidan 2011 and Zhang 2011) we respectfully disagree. This represents a factual error and requires correction. These two studies were definitely designed to detect for awareness as a primary endpoint. We do agree that the third study cited (Kerssens 2009) was not designed to detect anaesthesia awareness according to the accepted definition.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The three trials referred to in section 5.3 which were not designed to detect awareness did not include the studies by Avidan or Zhang studies. The trials referred to were by Kamal et al; Liao et al and Ellerkamn et al.

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45.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.12 We note in this section a review of seven randomized controlled trials comparing the clinical effectiveness of the E-Entropy monitor with standard clinical monitoring. ”Clinical effectiveness” assumes a measure of efficacy of treatment effect. The E-Entropy monitor has not been evaluated in large clinical trials specifically designed to test the efficacy of E-Entropy monitoring on awareness or in clinical trials designed to test the efficacy of these devices to reduce awareness compared to standard clinical practice or alternative measures. As stated earlier and supported by expert opinion, extension of the efficacy of BIS monitoring to E-Entropy is not justified.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee concluded that the three monitors are broadly equivalent.

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46.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.19 We note in this section a review of four randomized controlled trials comparing the clinical effectiveness of the Narcotrend monitor with standard clinical monitoring. ”Clinical effectiveness” assumes a measure of efficacy of treatment effect. The Narcotrend monitor has not been evaluated in large clinical trials specifically designed to test the efficacy of Narcotrend monitoring on awareness or in clinical trials designed to test the efficacy of this device to reduce awareness compared to standard clinical practice or alternative measures. Hence, the impact of the Narcotrend devices on reducing this adverse event remains unknown. As stated earlier and supported by expert opinion, extension of the efficacy of BIS monitoring to Narcotrend is not justified.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee were advised that comparative studies showed correlation between the index values produced with BIS monitoring and the values from E-Entropy or Narcotrend-Compact M monitoring. The Committee concluded that the three monitors are broadly equivalent.

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47.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.28 We notice that CE models developed by the NICE External Assessment Group may have overlooked the financial savings associated with reduction in the post operative time (eye opening, extubation, etc.) spent in the operation room and in the PACU, that were identified by the 2007 Cochrane review, and whose results were essentially confirmed by further studies. The Diagnostics Consultation Document notes this consideration in Section 6.8. Time savings were statistically significant irrespectively of the type of anaesthetic and patient group. Based on a study published by Paton and colleagues in 2010, average costs of £4.40 and £0.33 are associated to each minute spent in the operation room and in the PACU, respectively. According to the YHEC CE model, that would lead to an average saving of £45 per operation. We suggest the inclusion of the financial savings associated with reduction in postoperative time in the operating room and in the PACU into the model.	Thank you for your comment. The Committee considered this comment and decided to change section 6.10 of the guidance. The Committee considered incorporating the cost savings associated with reductions in operating theatre time and recovery time might improve the cost effectiveness of the monitors, but the time savings were too small to significantly benefit clinical practice.
48.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.29 The YHEC CE model focused on the general adult population allowing for separate analysis of under- and over-65 populations. The resource use and the rates of adverse reactions were adjusted to represent the general population. In fact, if acquired as a standard anaesthesia monitoring device in a given operation room, it is reasonable to assume that the BIS would be used for most patients undergoing total total-anaesthesia surgery in that operation room. The YHEC model assumed that at least 18% (based on Ghoneim 2009) of those who experience AR will also experience anxiety and other psychological symptoms requiring medical treatment or behavioral therapy at an average cost of £925 per case.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. No robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting were identified so scenario analyses were performed using data from the meta-analysis by Liu, 2004. The

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			The model was designed and populated to include health and economic outcomes of PO nausea and vomiting, delirium in the over 65 age group, and cognitive disorder, allowing also for the inclusion of potential effects on stroke and death, based on simple algebraic calculations informed by published studies (Nelskyla 2001, Selim 2007, and Leslie 2010).	scenario analyses showed that the incremental costs for BIS monitoring were reduced but the ICERs remained largely unchanged for all of the population groups. The Committee noted that the clinical benefits associated with avoiding excessively deep levels of anaesthesia may have been underestimated in th cost effectiveness analyses. The Committee also noted the uncertainty about the extent to which depth-of-anaesthesia monitoring could reduce the risk of excessively deep levels of anaesthesia.
49.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.30 The YHEC CE model focused on the general adult population allowing for separate analysis of under- and over-65 populations. The resource use and the rates of adverse reactions were adjusted to represent the general population. In fact, if acquired as a standard anaesthesia monitoring device in a given operation room, it is reasonable to assume that the BIS would be used for most patients undergoing total total-anaesthesia surgery in that operation room. The YHEC model assumed that at least 18% (based on Ghoneim 2009)	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. No robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting were identified so scenario

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			of those who experience AR will also experience anxiety and other psychological symptoms requiring medical treatment or behavioral therapy at an average cost of £925 per case. The model was designed and populated to include health and economic outcomes of PO nausea and vomiting, delirium in the over 65 age group, and cognitive disorder, allowing also for the inclusion of potential effects on stroke and death, based on simple algebraic calculations informed by published studies (Nelskyla 2001, Selim 2007, and Leslie 2010).	analyses were performed using data from the meta-analysis by Liu, 2004. The scenario analyses showed that the incremental costs for BIS monitoring were reduced but the ICERs remained largely unchanged for all of the population groups. The Committee noted that the clinical benefits associated with avoiding excessively deep levels of anaesthesia may have been underestimated in the cost effectiveness analyses. The Committee also noted the uncertainty about the extent to which depth-of-anaesthesia monitoring could reduce the risk of excessively deep levels of anaesthesia.

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<table>
<tr><th>Comment no.</th><th>Consultee</th><th>Section no.</th><th>Comment</th><th>Response</th></tr>
<tr><td>50.</td><td>Consultee 8 Manufacturer</td><td>Section 5 Comment on section 5: Outcomes</td><td>5.32 The YHEC CE model followed an approach similar to the one described in the NICE document for the calculation of the unit costs for depth of anaesthesia BIS monitor. This included the acquisition cost of the monitor and related components (annual cost assuming a five-year effective life for the Monitor, three-year life for the battery and two-year life for the PIC cable, and converted to an average cost per patient) and recurring costs arising from the single-use sensors.

<table>
<tr><th>Component</th><th>Market price</th><th>Average life span (yrs)</th></tr>
<tr><td>Monitor</td><td>£4,350.00</td><td>5</td></tr>
<tr><td>AMS BISx</td><td>£1,071.00</td><td>5</td></tr>
<tr><td>PIC cable</td><td>£121.80</td><td>2</td></tr>
<tr><td>Battery</td><td>£136.50</td><td>3</td></tr>
<tr><td>Sensor</td><td>£14.50</td><td>0</td></tr>
</table>
</td><td>Thank you for your comment. The Committee considered this comment and decided not to change the guidance. All of the costs for the BIS monitor used in this evaluation were provided by the manufacturer.</td></tr>
<tr><td>51.</td><td>Consultee 8 Manufacturer</td><td>Section 5 Comment on section 5: Outcomes</td><td>5.32 We note the cost of the GE sensor is mentioned but not the cost of the GE module. Although it is often provided as part of the package there must be a list price associated with it as per BIS and Narcotrend. Was this considered in the cost analysis?</td><td>Thank you for your comment. The cost of the GE module was included in the cost analysis.</td></tr>
<tr><td>52.</td><td>Consultee 8 Manufacturer</td><td>Section 5 Comment on section 5: Outcomes</td><td>5.34 The ICER values found by the NICE External Assessment Group may be overestimated, most likely as a result of underestimation of BIS-associated savings. Even when none of the complications of anaesthesia were</td><td>Thank you for your comment. The Committee considered this comment and decided not to change</td></tr>
</table>

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			included, the YHEC model found that, as a result of reduced use of anaesthetic and personnel time, the BIS would lead to a net saving of £36 per operation. When the sequelae of AR were included, the use of the BIS resulted in £37 savings and averted the loss of 0.012 QALYs per operation. When PO nausea and vomiting, delirium in the over-65 age group, and cognitive disorder were included, it lead to £75 savings and averted the loss of 0.013 QALYs per operation. If reductions in the incidence rates of anaesthesia related hemorrhagic-stroke and death were included, the model predicted £107 savings and averted the loss of 0.041 QALYs per operation.	the guidance. No robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting were identified so scenario analyses were performed using data from the meta-analysis by Liu, 2004. The scenario analyses showed that the incremental costs for BIS monitoring were reduced but the ICERs remained largely unchanged for all of the population groups. The Committee noted that the clinical benefits associated with avoiding excessively deep levels of anaesthesia may have been underestimated in the cost effectiveness analyses. The Committee also noted the uncertainty about the extent to which depth-of-anaesthesia monitoring could reduce the risk of excessively deep levels of anaesthesia.

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53.	Consultee 8 Manufacturer	Section 5 Comment on section 5: Outcomes	5.36 The results of the YHEC CE model proved robust to uni-variate deterministic and multi-variate probabilistic sensitivity analysis. For instance, the probabilistic sensitivity analysis showed that when all outcomes, with the exception of stroke and death, were considered the BIS would be cost-saving in 60% of the simulated cases, with a maximum cost of £70 per operation and with a maximum ICER of £3,406, significantly lower than the ICER values identified by the NICE External Assessment Group.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. No robust data to estimate the effect of BIS monitoring on post-operative nausea and vomiting were identified so scenario analyses were performed using data from the meta-analysis by Liu, 2004. The scenario analyses showed that the incremental costs for BIS monitoring were reduced but the ICERs remained largely unchanged for all of the population groups. The Committee noted that the clinical benefits associated with avoiding excessively deep levels of anaesthesia may have been underestimated in the cost effectiveness analyses and also noted the consequent uncertainty in the resulting ICERs.

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54.	Consultee 9 NHS Professional	Section 5 Comment on section 5: Outcomes	5 Our summary of Section 5 would be different. We conclude and suggest: (a) The available evidence on the impact of the technologies on reducing the likelihood of intraoperative awareness is limited. Overall, 'depth of anaesthesia' monitoring is not associated with a statistically significant reduction in intraoperative awareness in patients (perhaps arbitrarily) classified as at higher risk. Any reductions in general anaesthetic consumption, and decreased anaesthetic recovery times, compared with monitoring of clinical signs alone are all modest. (b) The cost effectiveness of depth of anaesthesia monitoring appears to be highly dependent on the incidence of awareness (and the latter will be better established by the NAP5 project). Indeed, we propose that these two suggested paragraphs replace current recommendation 1.1.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
55.	Consultee 2 NHS Professional	Section 6 Comment on section 6: Considerations	A majority of Council members viewed the failure to evaluate structured anaesthesia protocols based on end-tidal agent monitoring as a major flaw. This has been a minimum monitoring standard set by the AAGBI since 2007, is widely available, and would require very limited capital investment. The AAGBI will review its recommendations on monitoring in the light of the NAP5 study.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance.

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56.	Consultee 3 Manufacturer	Section 6 Comment on section 6: Considerations	As a side note on 6.4, I would like to mention that, according to our practical experience, the demand of inhaled anaesthetics (isoflurane, desflurane, sevoflurane, xenon) for maintaining an adequate depth of anaesthesia varies interindividually (similarly to intravenous anaesthetics). We observed that the individual demand was indicated by the EEG, but hardly by measurements of endtidal concentrations of inhaled anaesthetics.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
57.	Consultee 4 NHS Professional	Section 6 Comment on section 6: Considerations	Please see our comments on Provisional Recommendations 1.1 and 1.2. We recommend that paragraph 6.16 be amended to read: '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 muscle relaxants during anaesthesia and patients who are considered at higher risk of complications from general anaesthesia.'	Thank you for your comment. The Committee considered this comment and decided to add explanatory text to section 1 and add section 6.4 to the guidance..
58.	Consultee 5 NHS Professional	Section 6 Comment on section 6: Considerations	Depth of Anaesthesia Monitoring is uncommonly used in the UK. To recommend it would constitute a large shift in practice. Since many anaesthetists have read the literature, trialled BIS and similar, and have discarded them as unhelpful, a NICE recommendation is highly likely to cause confrontation with the target audience, and potentially cause a credibility issue for NICE.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.

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Comment no.	Consultee	Section no.	Comment	Response
59.	Consultee 6 Manufacturer	Section 6 Comment on section 6: Considerations	The Committee inaccurately considers that awareness during surgery can be reduced using structured anaesthesia protocols such as measuring ETAC. ETAC is only useful for patients received inhaled anaesthetics not intravenous or combined anesthetics. As previously stated alarms are neither routinely used nor standard clinical practice. --- Depth of anaesthesia monitoring is most likely to be cost-effective and of clinical benefit in patients receiving total intravenous anaesthesia as well as volatile and inhaled anaesthesia. Inhaled anesthetic cost was included as a model input parameter in the Diagnostics Assessment Report but appears to have been excluded from this interim analysis without explanation. BIS should be recommended as an option for reducing adverse outcomes from inhaled and combination anaesthesia administration in addition to total intravenous anaesthesia administration. The Cochrane review states that BIS monitoring reduces volatile anaesthetic usage (desflurane, sevoflurane, isoflurane) by 0.17 MAC equivalents. Since publication of the Cochrane review, no clinical studies comparing BIS monitoring to standard clinical practice as defined in the NICE Diagnostics Consultation document have demonstrated otherwise.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. --- Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered the cost-effectiveness analyses and concluded that the use of depth of anaesthesia monitoring was not cost-effective in patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia, but does recommend the use of these monitors for patients at higher risk of adverse outcomes.

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60.	Consultee 8 Manufacturer	Section 6 Comment on section 6: Considerations	6.4 The Committee considers that awareness during surgery can be reduced using structured anaesthesia protocols such as measuring ETAC. We respectfully disagree with this assumption/assertion. ETAC as a tool is only useful for patients received inhaled anaesthetics; not intravenous or combined anaesthetic administration. Statement 6.4 would be more correct amended to include "....such as measuring ETAC that incorporates audible alarms to actively alert the clinician of potential underdosing and utilizing a targeted dose of volatile anesthesia". However, as previously stated, alarms are neither routinely used nor standard clinical practice.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of structured ETAC protocols with audible alarms and concluded they were not representative of current routine NHS practice (standard clinical monitoring). Standard clinical monitoring included ETAC without audible alarms.
61.	Consultee 9 NHS Professional	Section 6 Comment on section 6: Considerations	6. Therefore, as a general comment on Section 6, we find many of the Committee's recommendations listed here as being at surprising variance with the objective evidence and also with their own considerations listed here. Specifically:	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.

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62.	Consultee 9 NHS Professional	Section 6 Comment on section 6: Considerations	6.4 This is at odds with the statement 4.6 made above, that "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". Only one of these statements can be true.	Thank you for your comment. The Committee considered this comment and decided to add sections 6.5 and 6.6 to the guidance. The Committee considered the use of structured ETAC protocols with audible alarms and concluded they were not representative of current routine NHS practice (standard clinical monitoring). Standard clinical monitoring included ETAC without audible alarms.

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63.	Consultee 9 NHS Professional	Section 6 Comment on section 6: Considerations	6.11 We take issue with this logic, which might be the focus of much future discussion about NICE's general approach on such matters. As written this paragraph indicates that a prior judgement has already been made – ie, that the technology is likely beneficial - and that the Committee's purpose is to use whatever evidence justifies that judgement. Science works the other way: No judgement at all can be made on likely benefits until the appropriate evidence is available. If the benefits are suspected to be strong, then this justifies the need to undertake large studies, etc; it does not justify a reason to adopt technology in their absence. The correct version of this sentence must therefore read: " The Committee considered the value of additional research studies before making its recommendations, and concluded that the size, complexity, cost, and time requirements of such studies are justified by the potential benefits to the NHS in establishing whether this is a beneficial technology."	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
64.	Consultee 9 NHS Professional	Section 6 Comment on section 6: Considerations	6.12 We fully agree with this paragraph. However, one comment notably absent which is a potential barrier to understanding consciousness and the monitoring of it is the proprietary nature of the algorithms used by manufacturers. At some point this will need to be challenged and this NICE report seems an appropriate opportunity. Therefore, we suggest adding the words: "Fully understanding how monitoring works - and how it provides an insight into anaesthesia and unconsciousness - may require open access to some of the proprietary algorithms underlying the technology".	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.

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65.	Consultee 8 Manufacturer	Section 6 Comment on section 6: Considerations	6.16 We note the Committee's consideration that depth of anaesthesia monitoring is most likely to be cost-effective and of clinical benefit in patients receiving total intravenous anaesthesia. We do not agree with the decision to exclude depth of anaesthesia monitoring for the clinical environment of volatile or inhaled anaesthetic administration. Inhaled anaesthetic cost was included as a model input parameter in the Diagnostics Assessment Report but appears to have been excluded from this interim analysis without explanation. We suggest BIS be recommended as an option for reducing adverse outcomes from inhaled and combination anaesthesia administration in addition to total intravenous anaesthesia administration. The Cochrane review states that BIS monitoring reduces MAC volatile anaesthetic usage (desflurane, sevoflurane, isoflurane) by 0.17 minimal alveolar concentration equivalents (MAC) (noted in Section 5.6 of the Diagnostics Consultation Document). Since publication of the Cochrane review, no clinical studies that have compared BIS monitoring to standard clinical practice as defined in the NICE Diagnostics Consultation document have demonstrated otherwise.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee considered the cost-effectiveness analyses and concluded that the use of depth of anaesthesia monitoring was not cost-effective in patients at general risk of adverse outcomes from anaesthesia receiving either intravenous or inhaled anaesthesia, but does recommend the use of these monitors for patients at higher risk of adverse outcomes.
66.	Consultee 9 NHS Professional	Section 6 Comment on section 6: Considerations	6.17 To this paragraph we recommend the words: "This training must go beyond simply manufacturer instructions on how to use the monitors, and include specialty training in the neuroscientific and philosophical basis of consciousness and in the psychological impact of accidental awareness upon patients."	Thank you for your comment. The Committee considered this comment and decided to change sections 1.4 and 6.20 of the guidance.

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67.	Consultee 2 NHS Professional	Section 7 Comment on Section 7: Proposed recommendations for further research	NICE will already be aware of the NAP5 study which will make a significant contribution to this area, thus large scale research is already in progress. NAP5 may remove much of the uncertainty in the evidence. Many Council members felt the scale of NAP5 to be sufficiently important that it should be incorporated in the Committees conclusion.	Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.
68.	Consultee 3 Manufacturer	Section 7 Comment on Section 7: Proposed recommendations for further research	It is appropriate not to delay the uptake of EEG monitoring. Hardware and software of the Narcotrend are continually further developed. In recent time this has been supported by a generous grant from the European Union to refine the classification algorithms, optimize the artefact detection, and to further develop hardware components. Parallel to innovations of the technology, studies on the clinical effects of EEG monitoring are performed.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
69.	Consultee 5 NHS Professional	Section 7 Comment on Section 7: Proposed recommendations for further research	Wait for NAP 5 to report before considering recommendations. Discuss and develop a standard tool for disgnosis (e.g MACI and Modified Brice have different questions) Also, reconsider the weaknesses of various published studies which used very lax recruitment criteria	Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.

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70.	Consultee 9 NHS Professional	Section 7 Comment on Section 7: Proposed recommendations for further	Like para 6.11 above, the last sentence of this paragraph erroneously implies it is justifiable to adopt a technology which is believed to be of benefit, before there is any persuasive evidence establishing its efficacy. The 'complications' of doing research in this area are not insurmountable at all. Rather, we would like to see NICE making a more robust case - rather than adopting a nihilistic tone - for research in this area. Anaesthetists could then use this as a driver with funding agencies to obtain the necessary support to do the studies which NICE agrees are essential. We would therefore ask NICE to refer back to our suggested revision of 6.11, above, and revise this whole paragraph to read: " The Committee encourages further research as described in section 6.12 but has made no specific research recommendations. This is because advising on specific research projects is outside the Committee's remit. The many complications in doing research in this area of anaesthesia are not insurmountable, and the Committee feels that the potential benefits of this technology (if it works) to anaesthetists, the NHS and to patients is such that research in this field should become a priority for future funding."	Thank you for your comment. The Committee considered this comment and decided not to change the guidance. The Committee encourages additional research into depth of anaesthesia monitoring and the clinical implications of unintended awareness during surgery and the impact of the depth of anaesthesia on short- and long-term morbidity and mortality. Recommendations for prioritising research funding are outside the Committee's remit.
71.	Consultee 2 NHS Professional	Section 8 Comment on Section 8: Implementation	THe AAGBI will be happy to work with NICE in this area.	Thank you for your comment.

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72.	Consultee 3 Manufacturer	Section 8 Comment on Section 8: Implementation	The Narcotrend group would like to participate in the development of tools for putting this guidance into practice.	Thank you for your comment.
73.	Consultee 2 NHS Professional	Section 9 Comment on Section 9: Related NICE guidance	Council members had no comment	Thank you for your comment.
74.	Consultee 2 NHS Professional	Section 10 Comment on Section 10: Review	The AAGBI would support regular review of the evidence, although remains concerned that the evidence may be skewed by the overall recommendations of the Committee.	Thank you for your comment. The Committee considered this comment and decided not to change the guidance.
75.	Consultee 9 NHS Professional		In summary, while we welcome the efforts NICE and its committees have made in studying the important question of monitoring unconsciousness in anaesthesia, there are several very important shortcomings. We do not feel that the advice proposed is supported by the evidence. Therefore we advise that it will likely be very controversial within the anaesthetic community. Given the activity related to our NAP5 project, and the important way in which those outcomes would help NICE's conclusions, we strongly advise postponement of these recommendations until after our project has completed. This would also present an opportunity for NICE and NAP5 to work in a more collaborative way in the generation of any outputs.	Thank you for your comment. The Committee considered this comment and decided to add section 6.15 to the guidance. The Royal College of Anaesthetists is a registered stakeholder for this evaluation.