National Institute for Health and Clinical Excellence

Depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend)

Diagnostics Assessment Report (DAR) - Comments

Responder reference no.	Comment no.	Page no.	Section no.	Comment	Response
1	1.	8	Heading of Table 109	Narcotrend *(spelling)*	
2	2.	11	Objectives	This section states that the objective of this report is to assess the clinical- and cost-effectiveness of BIS, E-Entropy and Narcotrend technologies. In contrast to the substantial evidence for the BIS monitoring technology, clinical and cost-effectiveness data specific to E-Entropy and Narcotrend is very limited. This is particularly true for the clinical impact of reducing the incidence of awareness. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	3.	12	2 Economic Evaluation	While we recognise that this area can be complex we feel that the assessment group have not balanced the economic model to reflect all key variables that might impact on the cost-effectiveness. Even within this brief description of the model, there is a clear focus on intra-operative awareness and subsequent LPS and PTSD. These variables are important and reflect	

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				the associated consequences of under-sedation, however there is much less focus on the potential implications of over-sedation such as PONV and POCD and the implications these can have on the efficiency of the operating theatre. As noted in later comments (comment 15, 39, 53, 60) we do not feel that these variables have been given as much weight in the analysis as they should and hope that the Committee will explore these variables in more detail within in their discussions.	
2	4.	13 (also p.41, Tables on p.55, 101, 189 and others)	Results, paragraph 1, p. 13	"*22 RCT's comparing BIS, E-Entropy and Narcotrend.....15 trials of BIS, 7 trials of E-Entropy, and 4 trials of Narcotrend.....The Cochrane review of BIS included 31 RCTs."* These pages and several others within the DAR note the significant quantity of BIS outcomes research compared to the other technologies evaluated. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies. Scientific conclusions are more powerful with a larger number of trials providing more sampling and data.	

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3	5.	14	2 Results	In describing the results of the trials on intraoperative awareness with respect to the different anaesthesia approaches towards the end of page 14, we feel it is important to highlight to the Assessment Group and Diagnostic Assessment Committee the relevance of these different approaches within the UK. The use of inhaled only anaesthesia is primarily for paediatrics and adults who are difficult to intubate, who represent a minority of patients within the UK setting. In the UK, the majority of patients for whom this evaluation will be most relevant are for those receiving mixed anaesthesia or TIVA. We believe these groups combined will represent over 80% of the potential population being considered within this evaluation.	
2	6.	15	Results, paragraph 1, p. 15	*"None of the trials reported the longer-term detrimental impact of awareness, though one did report patient distress and sequelae as a post hoc secondary outcome."* Although this statement is correct regarding the initial trials, there are data and references in the literature and within the DAR that describe long term follow-up and consequences of intra-operative awareness in the B-Aware trial. There are also references to general long term sequelae of intraoperative	

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				awareness. Please consider revising to state that the long-term detrimental impact of awareness has been reported, according to content contained herein on Pages 128 & 129 Table 50, Cited publications; Leslie K, Chan MTV, Myles PS, Forbes A, McCulloch TJ. Posttraumatic stress disorder in aware patients from the B-Aware trial. *Anesthesia and Analgesia* 2010; 110(3):823-828.; Lennmarken C, Bildfors K, Enlund G, Samuelsson P, Sandin R. Victims of awareness. *Acta Anaesthesiologica Scandinavica* 2002; 46:229-231.	
2	7.	15	Results, paragraph 2, p. 15	*"Post-operative nausea and vomiting (PONV) was reported in a handful of trials, and there were generally no statistically significant differences between groups."* Per the Liu meta-analysis (2004), there is evidence of impact of BIS monitoring on PONV in ambulatory surgery. Similar to the approach with clinical effectiveness of brain monitoring on reducing awareness in different potential patient populations, the PONV benefit in ambulatory patients may need to be assessed according to patient type. The authors should state that there are limited RCTs	

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				for Entropy and Narcotrend looking at any of the endpoints described in this paragraph.	
3	8.	15	Systematic review of cost-effectiveness, paragraph 3, p. 15	This paragraph singles out one publication of the 134 examined and states the conclusion that BIS monitoring does not appear cost-effective. Of note, this publication (98) did not include any primary data. The B-Aware study did include a cost-effectiveness estimate based upon their effectiveness data in patients at increased risk for awareness, and found a NNT of 138 and a cost of $2200 to avoid one case of awareness in similar patients. We suggest it be noted in this section/ paragraph that there was an absence of appropriately powered clinical studies to measure the clinical or cost-effectiveness of the E-Entropy and NarcoTrend technologies to impact the incidence of awareness.	
2	9.	17	Entropy compared with standard clinical monitoring: paragraph 3, p. 17.	*"In the absence of evidence specific to Entropy we have applied the effectiveness estimates derived for BIS.....modelled clinical effectiveness of Entropy was identical to that reported for BIS....Entropy monitoring was associated with improved outcomes, based on applying clinical effectiveness evidence reported for BIS".* Fundamentally, this strategy to apply clinical	

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				effectiveness from one technology to another is flawed. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
2	10.	18 - 19	Narcotrend compared with standard clinical monitoring	*"Insufficient evidence was identified to estimate the effectiveness of depth of anaesthesia monitoring with Narcotrend on the incidence of intraoperative awareness or on post-operative cognitive dysfunction. In the absence of evidence specific to Narcotrend we have applied the effectiveness estimates derived for BIS, described above."* Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	11.	18	2 Entropy	It should be noted that for high risk patients undergoing TIVA in all cases but one the ICER remained below the upper cost-effectiveness threshold of £30,000 and in many cases below the £20,000 cost-effectiveness threshold.	
3	12.	18	2 Entropy	It should be noted that for high risk patients undergoing mixed anaesthesia, in the majority of	

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				cases the ICER remained below the upper threshold of cost-effectiveness of £30,000.	
2	13.	20	Conclusions, paragraph 1	"*the available evidence on the impact of the technologies on reducing the likelihood of intraoperative awareness is limited.*".. Given the body of published evidence on the BIS technology, we suggest that this statement should be specific to the E-Entropy and Narcotrend technologies.	
2	14.	20	Conclusions, paragraph 1	*"Overall, BIS was not associated with a statistically significant reduction in intraoperative awareness in patients classified as at a higher risk".* This conclusion statement seems at odds with the DAR statements on Page 14: *The six trials of patients classified with risk factors for intraoperative awareness, all of which evaluated BIS, were combined in a fixed effect meta-analysis. The overall pooled Peto Odds Ratio was 0.45 (95% CI 0.25, 0.81) in favour of BIS.* Although the DAR has sufficient framing of this result due to the heterogeneity of the trials, this remains an important observation that BIS WAS associated with a significant reduction in patients classified at high risk.	

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3	15.	20	2 Conclusion	It is noted that the reduction in general anaesthetic consumptions and decreased anaesthetic recovery times may be considered clinically modest. We would suggest that while these variables may be considered to be of modest clinical value, they can represent important economic and efficiency gains for the hospital. It has been noted on page 83 that for the majority of outcomes measured to assess recovery time there is a significant reduction associated with Entropy. While these reductions may not appear important individually, we fully believe when they accumulate over a full day of surgeries such reductions can facilitate keeping to the daily operating schedule. Delays in recovery can have a knock-on effect with late starts for subsequent surgeries, and in a worst case scenario perhaps result in cancellation. The financial implications of late-starts and cancellations can be significant to the individual hospital, let alone to the NHS as a whole. We hope the following examples will demonstrate the potential importance of these factors and therefore the potential benefit that Entropy can provide. A presentation by Jason Smith on Evidence Based Scheduling looked at operating theatre improvements	

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				in his hospital (West Middlesex University Hospital). It was noted that over-runs cost £66,000 per month, but by abolishing late-starts this could be reduced to £35,000 per month. The use of Entropy can significantly impact on recover times, etc. which would logically contribute towards the abolition of such late-starts. See attachments in separate document (Royal College of Surgeons presentation.pdf) The NHS Institute for Innovation and Improvement considered improving quality and efficiency in the operating theatre. It was noted that if contact time (total anaesthetic and surgical time) was increased as a % of total scheduled time by 10% this could lead to an annual efficiency saving of £3,168,000. This is another example demonstrating the importance of variables such a reduction in recovery time which can contribute to increases in contact time and therefore potential improvements in theatre efficiency. See attachments in separate document (Finance leaflet.pdf) Finally, the Department of Health note that in Q3 2011, 14,683 elective operations were cancelled for non-clinical reasons. See attachments in separate document (dh_132597.xls)	

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3	16.	20	2 Conclusion	While the evidence on impact of technologies on reducing the likelihood of awareness is limited we believe that there is sufficient evidence to demonstrate at least clinical potential. Looking at Figure 2, page 60 the results of the meta-analysis show a significantly favourable reduction on awareness. While there is heterogeneity, we also feel it is worth noting the results of the individual studies in those patient groups relevant to the UK, specifically those receiving either mixed or TIVA anaesthesia. In both these large RCTs the EEG monitor significant reduced awareness compared to standard clinical monitoring. While caution is advised when interpreting the results of the meta-analysis due to heterogeneity, we would encourage the Committee to consider the results of the individual studies as a demonstration of clinical benefit.	
3	17.	20	2 Conclusion	Caution is indeed required when undertaking an evaluation of this type however we feel that given the available data and the sensitivity analysis completed by the assessment group, there is increased confidence in the cost-effectiveness potential especially for high risk patients.	

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2	18.	27	3.2.1: paragraph 2	*"such as those manufactured by ..."* Please add GE Healthcare and Mindray (Philips, GE, Dräger, and Mindray are the 4 largest monitoring companies in EU and globally.)	
1	19.	28	3	*The Narcotrend does not provide a visually classified EEG, that can only be done by a human expert. Visually classified EEGs were the basis for the development of the multivariate classification functions used in the Narcotrend. Therefore we suggest to write:* Multivariate statistical methods using proprietary pattern recognition algorithms are then applied to these parameters to provide an automatically classified EEG. The basis for the development of the automatic classification functions were visually classified EEGs. The classification scale is from …	
1	20.	28	4	Narcotrend *(spelling)*	
2	21.	29	3.2.5	Please add additional BIS artefact detection wording per "Monitoring Consciousness During Anesthesia and Sedation: A Clinician's Guide to the Bispectral Index® (Scott D. Kelley, MD, author)*:* Some of the steps involved in the analysis of the EEG	

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				include multiple methods of artifact detection and processing. Segments of the EEG that are compromised by the presence of artifact are not included in the calculation of the BIS Index. BIS monitoring systems utilize a variety of signal analysis methods to detect and reduce extraneous artifacts that contaminate the EEG. In fact, many of the improvements in the BIS system over the past decade have been in the area of artifact processing. With the development and release of the BIS-XP system, the performance and reliability of BIS have been substantially improved, especially in the presence of electrocautery artifacts. The BIS Monitoring System is designed to provide only highly reliable data by removing signal that is detected as artifactual.	
2	22.	30	1	Narcotrend *(spelling, 2x)*	
2	23.	33	4.1.1, paragraph 2	*"Scoping searches indicated that the volume of evidence for BIS was relatively larger than for Narcotrend and Entropy…"* The BIS volume of evidence is significantly larger than that for Narcotrend or E-Entropy. Scientific conclusions are more powerful with more	

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				sampling/data.	
3	24.	33	4.1.1	Systematic review based on a previous Cochrane systematic review – while this seems practical what measures were taken to ensure the approach taken in the Cochrane review was also appropriate for this review (for example the objective of the Cochrane review does not include post-operative cognitive dysfunction which is an outcome of this evaluation therefore there may be relevant data that is not included in this evaluation simply because it was not an objective of the previous Cochrane review).	
3	25.	35	4.1.2	There is an implication within the study design paragraph that non-RCT data will not be considered if RCT data is available. We believe this is a fundamental flaw in any evaluation as it is possible to have poorly designed RCTs which might not fully reflect the efficacy of a product while there may be well designed non-RCTs that can provide significant information on effectiveness to the discussion. If well-designed non-RCTs are available we would suggest that these also be considered to provide further information to help inform decisions. If the assessment group have considered non-RCT studies	

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				it might be appropriate to note this within the report more explicitly. Please see attached in a separate document an updated reference list that has just become available to us on Entropy.	
2	26.	39	4.3.1, base case	*"Where data from the systematic review of patient outcomes were insufficiently robust or where no evidence specific to the technology being considered was been identified data derived for other included technologies were used to populate the model."* Again, this approach seems to take a non-evidenced based approach to technology assessment. If there is no evidence specific to a technology, an alternative approach is to not extrapolate the effectiveness measures from another technology. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	27.	39	4.3.1	We would appreciated further clarification on why the assumption that potential benefits of reduced anaesthetic dose and reduction in anaesthetic-related complications are only included in the base-case of the general surgical population? It is noted on page	

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				124 that as there is a raised risk of awareness in high risk group, this may be an indication that this group of patients are already at a risk of being under-dosed. We would suggest that this higher risk of awareness would actually result in a tendency for over-sedation therefore the use of depth of anaesthesia monitors in this high risk group would impact on consumption of anaesthetics.	
2	28.	51	Technologies, end of paragraph 1	*"Given the variability in reporting it is not clear how comparable the trials are in terms of the software and BIS algorithms used, which may have implications for the interpretation of the results of the trials."* The BIS technology has undergone periodic changes to software and algorithm with the specific goal of enhancing clinical performance, particularly with artefact detection and processing. Major revisions to the algorithm were cleared via the FDA 510(k) process to support substantial equivalence to the predicate BIS device. This type of substantial equivalence minimizes the need for concerns about interpreting trial results.	
2	29.	53	Technologies; paragraph 1, p. 53	*"The trial by Avidan and colleagues reported that summaries of BIS and ETAC protocols were given to the practitioners to provide education and to increase*	

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				adherence. Furthermore, signs were affixed to anaesthesia machines to remind practitioners to check BIS/ETAC and consider patient awareness." It is important to emphasize the strengths as well as weaknesses of the Avidan trial results. Although this result demonstrates that an "ETAC protocol" has substantial efficacy to reduce awareness, it is important to note that Avidan's ETAC protocol is not standard practice, nor is it the clinical monitoring standard identified as the comparator in this evaluation (see the clinical monitoring standard, page 11, which includes tachycardia, hypertension, sweating, lacrimation, movement/grimacing, and tachypnea).Avidan results must be viewed within the context of comparing two alternative intervention strategies to reduce awareness in high-risk patients. Furthermore, the protocol and alarm implementation in the Avidan trial may have a design effect on the study and should not be compared to, or portrayed as "standard practice". A major weakness of this study is that a true "standard practice" cohort was not collected for comparison. BIS and ETAC monitoring were compared to expected standard practice incidence and also to each other. Consequently the study discussion focused primarily on the comparison of two non-standard approaches for monitoring	

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				intraoperative awareness to each other, and both approaches (BIS & ETAC) showed a statistically significant reduction in awareness incidence compared to expected incidence.	
2	30.	57	Outcomes; paragraph 2, p. 57	*"This study [Avidan et al] was designed specifically to evaluate the effects of BIS on intraoperative awareness....."* It would be better to state that the study was designed to test alternative strategies to reduce awareness: BIS-guided care versus "ETAC-guided care". Avidan et al did not enroll a standard practice control group in this study. The BIS study group was compared to an ETAC protocol, not standard practice. Both BIS and the ETAC methods showed a statistically significant reduction in awareness incidence compared to expected incidence under standard practice.	
2	31.	59	Intraoperative awareness; paragraph below table	*"…there was a higher percentage of both definite awareness, and of definite or possible awareness cases in the group who received BIS monitoring than the group who had standard monitoring."* Caution about using the term "standard monitoring" to	

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				describe the cohort of patients randomized to receive the "ETAC protocol" with monitoring, alarms and target anesthetic concentration.	
2	32.	68	Post-operative nausea and vomiting	*"PONV was not reported in the Cochrane BIS review".* Although PONV was not an outcome measure of the Cochrane BIS review, an earlier meta-analysis (Liu, 2004) did find evidence of impact of BIS monitoring in ambulatory surgery. Similar to the approach with clinical effectiveness of brain monitoring on reducing awareness in different potential patient populations, the PONV benefit in ambulatory patients may need to be assessed according to patient type. Similar evidence has not been published for the Narcotrend or E-Entropy technologies.	
2	33.	71	Last bullet	*"...non-significant effects in the sub-group of patients receiving only inhaled anaesthesia..."* This paragraph needs additional reframing. The subset of studies of patients receiving only inhaled anaesthesia includes the Avidan studies where it was not merely monitoring, but a protocol of a target range of end-tidal volatile anesthetic administration. Thus the comparator group of "patients receiving only	

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				inhaled anesthesia" is markedly different because the impact of BIS was not tested versus "standard practice" but rather versus an alternative intervention strategy designed to reduce awareness (by aiming to administer a sufficient concentration of anesthetic - -.7-0.8MAC known to produce adequate suppression of memory formation). The ETAC protocol is not standard practice, nor is it the clinical monitoring standard identified as the comparator in this evaluation (see the clinical monitoring standard, page 11, which includes tachycardia, hypertension, sweating, lacrimation, movement/grimacing, and tachypnea).	
2	34.	71-85	5.1.4-5	It seems somewhat biased to use the apparently generic "entropy" term throughout this section to refer to cases in which Entropy monitoring (GE Healthcare) was the monitoring technology. Like BIS and Narcotrend, the study of specific technologies should be referenced as by the manufacturer "Entropy" not "entropy". The DAR should realize that Datex/Ohmeda was acquired by GE Healthcare – similar to the acquisition of Aspect Medical Systems by Covidien, but the BIS technology, like the Entropy technology continues following these acquisitions.	

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2	35.	72	5.1.4	The description of the target Entropy values, and the use of State Entropy (SE) or Response Entropy (RE) is not clear.	
2	36.	77 and Table 16, p. 78	5.1.5 4th para (last bullet)	*"Only one case of intraoperative awareness was reported in the six trials that measured this outcome (Table 16)."* Although the 6 trials report the occurrence of awareness, the cited trials are insufficient to provide an assessment of the ability of E-Entropy monitoring to influence the incidence of awareness. The study designs and protocols were not powered or designed to assess the occurrence of intraoperative awareness and it was not a primary defined endpoint of the study. Any such findings are inconsequential and should not be used to define awareness occurrence by E-Entropy. There are no clinical trials with the primary outcome of intraoperative awareness for E-Entropy.	
2	37.	78	Summary of Entropy assessment, 2nd bullet	*"Consumption was significantly lower in the entropy monitoring than standard clinical practice groups of all trials, with the proviso that in one of these trials the difference in sevoflurane consumption was statistically significant…"*	

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				In these 6 trials, the protocols were not designed to assess the occurrence of intraoperative awareness and it was not a primary defined endpoint of the study. Any such findings are inconsequential and should not be used to define awareness occurrence by E-Entropy. There are no clinical trials with the primary outcome of intraoperative awareness for E-Entropy.	
2	38.	84	Analgesic consumption; last bullet p. 84	*"Entropy monitoring had no consistent impact on other outcomes that were monitored, including intraoperative awareness, but the small sample sizes in the trials may not have provided adequate statistical power to detect meaningful differences in rare events…..the majority of the outcomes were secondary and may not have been adequately powered statistically to detect clinically relevant differences between the entropy and SP groups".* The important messages within this final bullet, along with the paucity of studies for E-Entropy and Narcotrend, should be emphasized by the authors in the Executive Summary and in the Conclusion. Scientific conclusions are more powerful with a larger number of trials providing more sampling and data.	

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3	39.	84	5.1.5	E-Entropy favours shorter time to discharge to and from the PACU however this is noted as of unclear clinical importance. We would highlight to the assessment group and the Committee that the shorter time to discharge is important from an efficiency and economic perspective (see Comment 16 for further detail). A patient cannot be moved from the OR to PACU until they are responsive to verbal commands and can maintain their own respiration. Delays in this initial recovery time in the OR can accumulate and in a worst case scenario may result in a cancelled surgery later in the day due to insufficient time available before staff leave. Similarly, if the PACU becomes overloaded it can cause delays in the operating room because the patient has to be recovered in the theatre while waiting for bed space in the PACU. These aspects are perhaps not well quantified in published literature but are a very real consideration for the operating staff and hospital. In a presentation by James Clarke – The Productive Operating Theatre (see attachment associated with Comment 16 Royal College of Surgeons Presentation), it is suggested that the PACU represents the largest cost component for hip and knee replacement surgery (1.5 hrs of PACU cost	

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				£3000, compared to the cost of surgery at £800). This demonstrates the potential cost implications associated with delays in the PACU.	
2	40.	87	5.1.7 Intraoperative Awareness	*"No patients in any of the trials of Narcotrend reported intraoperative awareness as explicit memory…"* This anecdotal reporting of lack of an occurrence of awareness in low risk patient populations should not be implied as stating clinical efficacy. There are no clinical trials with the primary outcome of intraoperative Awareness for Narcotrend.	
2	41.	91	Summary of Narcotrend assessment, 1st bullet	We suggest it be mentioned within this bullet that the awareness outcome was a secondary measure in the studies evaluated. The studies were also not adequately powered to measure this endpoint. This context is mentioned in the summary bullet point but should be stated explicitly within this bullet.	
1	42.	91	Points 5 and 7	Narcotrend *(spelling)*	
2	43.	92	5.2.1	See earlier comments regarding Abenstein's "study" – actually a model test of cost to avoid intraoperative awareness. The B-Aware projection of cost to avoid	

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				awareness should be included. Based upon the checklist in Table 29, it is hard to accept this model as a sufficient and reproducible cost analysis. As noted in the summary statement on 5.2.3, appropriate limitations are in place, yet the conclusions of this model exercise are also included in the executive summary.	
2	44.	94 - 95	5.2.2: bottom of p. 94/top of p. 94	"*They used estimates of the incidence of IR by averaging the difference between the Myles and colleagues and Avidan and colleagues".* The Abenstein model is also using the Avidan studies which incorporate ETAC as a comparator for BIS in his studies. ETAC monitoring is not standard practice, nor is it the clinical monitoring standard identified as the comparator in this evaluation (see the clinical monitoring standard, page 11, which includes tachycardia, hypertension, sweating, lacrimation, movement/grimacing, and tachypnea).	
2	45.	94	5.2.2; Last paragraph	Re: cost per patient of BIS monitoring, it should be noted that the unilateral sensor is the standard for general anaesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors.	

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2	46.	96	5.2.2, paragraph 1, p. 96	*"Each of the short term anaesthetic-related complications could be associated with additional treatment costs (such as anti-emetic medication for patients experiencing PONV…"* PONV "treatment" is frequently also associated with treatments including include hydration, multiple anti-emetic medications, delayed post-operative discharge and extended recovery time. All may be significant cost-related factors.	
2	47.	97	Model Parameters: Cost of depth of anaesthesia monitoring	*"The costs of depth of anaesthesia (DoA) monitoring consists of the capital costs associated with acquisition of the module and recurring costs associated with sensors which are attached to the patient"* It should be noted that the BIS unilateral sensor is the standard for general anaesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors. A similar weighted average of BIS Vista and BIS Vista Bilateral monitors should be performed.	

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1	48.	97	Table 31	*In the manufacturer`s submission the prices for the monitor and the electrodes were stated with the addendum "ca.", meant was "approx.". Please quote accordingly.*	
3	49.	97	5.3.2	The assessment group have made an assumption that the useful life of a monitor is 5 years. We would suggest that a more realistic estimate for this would be 7 – 10 years. We would request that the assessment group re-run the model to see the impact of this on the ICERs.	
1	50.	98	3	*"Narcotrend models require … (ICU)."* *Please add the following sentence:* The technical part of the training (handling the Narcotrend device, electrode placing) requires less than one hour.	
1	51.	98	4	*The words "in real" were omitted. Please write:* … that it can also send data in real time to other …	
2	52.	104	Post-operative nausea and	*"A baseline risk of PONV (30%)….We assumed that all treatments (such as prophylaxis against PONV) were the same for each monitoring group, and that all patients experiencing PONV were treated using 4 mg*	

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			vomiting	*ondansetron by intramuscular or slow intravenous injection".* A Unit cost = £5.39 is indicative of prevention or prophylaxis only and is not reflective of PONV treatment as seems to be indicated in this statement. Prophylaxis of PONV is significantly different in cost and scope of care to treatment of actual PONV and additional costs can be significant, not only patient care but to the patient care system and satisfaction. PONV treatment (as opposed to only prophylaxis) may often require multi anti-emetics, hydration, delayed discharge, additional nursing time, and prolonged hospital stays. These cost need to be factored into the "treatment" of PONV. The representation of "patient experiencing PONV" as a single drug administration is not representative of the costs associated with treatment for the "occurrence" of PONV. Prophylaxis prevention is not the same as "treatment for the occurrence". See: Cochrane Review 2007 and citations: Song D, Joshi GP, *et al*. Titration of volatile anesthetics using bispectral index facilitates recovery after ambulatory anesthesia. *Anesthesiology.* 1997;87:842-8.; Nelskyla KA, Yli-Hankala AM, *et al*. Sevoflurane titration using bispectral index postoperative vomiting in phase II	

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				recovery after ambulatory surgery. *Anesth Analg*. 2001;93:1165-9.	
3	53.	104	PONV	While we recognise that the data on PONV is limited the importance of this variable should not be overlooked. While the assessment group have included a cost for the treatment of PONV this only includes the cost of pharmacological treatment. Some cases of PONV can lead to an extended stay in PACU, and for some day-case surgeries, the incidence of PONV may be sufficient to lead to an overnight stay and associated costs. We believe that this should be factored into the costs associated with PONV as this will be especially relevant for the scenario analysis around impact on PONV. One paper we located noted a study that revealed the time to discharge was increased by 25% in patients with PONV. (See attachment in separate document McCracken 2008.pdf)	
2	54.	109	Change in incidence of intraoperative awareness; paragraph 1	*"There are no entries for entropy and Narcotrend in this table as insufficient data were identified in the systematic review of patient outcomes to derive robust results. As a result the relevant odds ratios derived for BIS were used in the model to estimate the impact on intraoperative awareness of depth of*	

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				anaesthesia monitoring with Entropy and Narcotrend." We strongly believe that this represents a flaw in the DAR. If there is insufficient evidence for a particular technology, the model should not include an impact from another technology.	
3	55.	123	5.3.2 Table 47	Are the proportions within this table listed correctly as they do not seem to correlate to the cost column for all of the rows?	
3	56.	124	5.3.2 Summary	We would request additional clarification on the justification for only assuming the reduction in consumption of anaesthetic for the general surgical population only. Please refer to comment 12 for additional information.	
2	57.	125	Table 48 + Tables 53 - 59	It should be noted that the BIS unilateral sensor is the standard for general anesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors.	
3	58.	126	5.3.2 Table 49	We would question the assumptions used to estimate the baseline costs of inhaled anaesthetics for all of	

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				the modules. The cost per MAC for specific inhaled anaesthetics demonstrates that there is a difference between the type of anaesthetic used, taking into account the potency of the agents (Table 34, page 100). However, the assessment group have then applied the proportionate change noted in Table 35 to the baseline cost associated with the studies for each individual monitor. It should be noted that the baseline cost of anaesthetic is related to the type of surgery being conducted, not the type of depth of monitor being used. It would seem more appropriate to assume an average length of operation to estimate the baseline inhaled anaesthetic costs for all monitors and then apply the specific proportionate reductions in inhaled anaesthetics to each monitor to more accurately reflect the impact of each monitor.	
3	59.	128	5.3.2 Table 50	Is the confidence interval for the reduction in awareness using depth monitor (high risk patients undergoing TIVA) – correct? Values do not correlate with Table 40 on page 109, nor Table 60 on page 136. In addition, within this table it notes that the cost associated with LPS is assumed to be £0. Can the assessment group provide further justification of this assumption? Admittedly the largest cost component	

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				of LPS costs will be associated with the incidence of PTSD which is included in the model but we would assume for those patients with LPS who do not go on to have PTSD there may be some healthcare associated costs such as GP visits, medication etc. It may be difficult to get a value for this but perhaps it should be something considered in the sensitivity analysis or scenario analysis.	
2	60.	130	Model input parameters, unit cost of PONV	*"Unit cost of PONV = £5.39 (4 mg of ondansetron)"* A Unit cost = £5.39 is indicative of prevention or prophylaxis only and is not reflective of PONV treatment as seems to be indicated in this statement. Prophylaxis of PONV is significantly different in cost and scope of care to treatment of actual PONV and additional costs can be significant, not only patient care but to the patient care system and satisfaction. PONV treatment (as opposed to only prophylaxis) may often require multi anti-emetics, hydration, delayed discharge, additional nursing time, and prolonged hospital stays. These cost need to be factored into the "treatment" of PONV. The representation of "patient experiencing PONV" as a single drug administration is not representative of the costs associated with treatment for the "occurrence"	

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				of PONV. Prophylaxis prevention is not the same as "treatment for the occurrence".	
3	61.	130	5.3.2 Table 51	PONV: As noted in comment 14 we believe that the cost associated with PONV is an under-estimate given the possibility that patients experiencing PONV may also be associated with increased length of stay in the hospital.	
3	62.	130	5.3.2 Table 51	POCD: there is no unit cost associated with POCD which we feel does not reflect the potential impact of this outcome. In a study by Slater et al 2007 'Cerebral Oxygen Desaturation Predicts Cognitive Decline and Longer Hospital stay after Cardiac Surgery', Annals of Thoracic Surgery 2009, it is noted that amongst other factors, patients with POCD had a significantly prolonged hospital stay. In addition, it was described in Ouellette 2010 that POCD could result in increased patient length of stay and hospital costs. We suggest that at the very least a cost implication associated with POCD should be included in the sensitivity analysis. See attachments in separate document (Slater 2009.mht and Ouellette.pdf).	

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3	63.	136	5.3.2 Table 60	How can the range associated with the duration of PTSD in Table 60 be 5.6 years to 9.6 years when the default is 12.7 years as noted in Table 50 page 129. The probability of PTSD in Table 50 is 0.177 (0.113 – 0.230) however the range noted in Table 60 is different. What exactly do the figures in Table 60 represented (it is noted a proportion PTSD rather than probability, could further clarification be provided). These inconsistencies/ lack of clarity in the tables make it difficult to fully review the results of the cost-effectiveness model. Did the assessment group consider variation in the cost of PTSD within the sensitivity analysis? A US study published in 2009 (Assessing Combat Exposure and Post-Traumatic Stress Disorder in Troops and Estimating the Costs to Society, Terri Tanielian) noted considerable differences in the cost of PTSD dependent upon the severity. For example, for PTSD and major depression the cost per case over 2 years ranged from $12,427 to $16, 884. In the assessment group model the duration of PTSD was assumed as 12.7 years, therefore the cost estimate of £9, 104 may be a considerable under-estimate.	

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				While this is US specific data and actual costs are not generalizable to the UK it may be appropriate to vary the included cost of PTSD ± 20% to determine the sensitivity of the ICER to this variable. See attachment in separate document (RAND_CT321.pdf)	
2	64.	143	Table 67 and 1st para	*"Inclusion of the impact of PONV with BIS monitoring into the base case analysis is unlikely to substantially affect decisions based on cost effectiveness criteria."* We respectfully disagree. Basing the cost-effectiveness model on a unit dose of ondansetron (Unit cost = £5.39) is indicative of prevention or prophylaxis only and is not reflective of PONV treatment as seems to be indicated in this statement. Prophylaxis of PONV is significantly different in cost and scope of care to treatment of actual PONV and additional costs can be significant, not only patient care but to the patient care system and satisfaction. PONV treatment (as opposed to only prophylaxis) may often require multi anti-emetics, hydration, delayed discharge, additional nursing time, and prolonged hospital stays. These cost need to be	

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				factored into the "treatment" of PONV. The representation of "patient experiencing PONV" as a single drug administration is not representative of the costs associated with treatment for the "occurrence" of PONV. Prophylaxis prevention is not the same as "treatment for the occurrence". The Liu meta-analysis (Anesthesiology 2004) estimated the cost of treating PONV as an average incremental cost for one additional nausea- and vomiting-free patient was40.49 USD.	
2	65.	pp. 149 – 169	Entropy compared with Standard clinical monitoring	We wish to reiterate that, absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	66.	155	5.3.3 Table 84	We are very encouraged by the results of the deterministic sensitivity analysis for the high risk patients undergoing TIVA as in only one instance (that of the lowest probability of awareness) did the ICER go above £30,000 and in the majority of cases the ICER remained below £20,000. We fully believe that the effectiveness of Entropy around awareness is equivalent to BIS (see justification in comment 3) and if coupled with the additional weight that we feel other	

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				parameters should have within the model (time to recovery, PONV, POCD etc), we feel that the potential benefit of Entropy to be both clinically and cost-effective for high risk patients undergoing TIVA is demonstrated.	
3	67.	156	5.3.3 Table 85	The results of the one-way sensitivity analysis of Entropy for general surgical patients provided a number of results just over the upper threshold of cost-effectiveness of £30,000. However we feel if the assessment group could consider some of the points raised in previous comments such as the potential costs associated with PONV, POCD, impact of recovery time etc. that the cost-effectiveness model would be more balanced and reflect the real potential of Entropy. Inclusion of these cost parameters would also likely bring down the ICER to more acceptable levels across the range of possible data variations as identified in the deterministic sensitivity analysis.	
3	68.	159	5.3.3	While the one way sensitivity analysis of Entropy in high risk patients undergoing mixed anaesthesia was more mixed that for high risk patients undergoing TIVA, we still feel encouraged that in the majority of analyses the ICER was below £30,000 and in many cases below £20,000. This again demonstrates the potential benefit of entropy to be cost-effective for	

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				high risk patients.	
3	69.	160	Table 88	We are encouraged by the results of the one way sensitivity analysis of Entropy in general surgery patients undergoing mixed anaesthesia. In all but two instances the ICER remained below the upper threshold level of £30,000. As noted previous in comment 67, we believe if some of our prior comments on other outcomes can be taken into effect within the model (those not specific to awareness) this will result in a more balanced model and reflect improved results for Entropy.	
3	70.	161	Scenario analysis	The scenario analysis considering the higher risk of awareness associated with a high risk population brings the ICER for Entropy down considerably and reinforces the potential value of this product given the consistency of the cost-effectiveness results across the range of input possibilities.	
3	71.	164	Scenario analysis	It is noted that in the scenario analysis for the general surgical population the base case estimate of probability of awareness is replaced by an extremely high and low value. The low value in this instance refers to the Pollard et al paper. We would like to highlight to the assessment group and Committee that we have found one possible explanation for this	

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				extremely low estimate. The US Anesthesia Awareness Registry (AAR) noted that one explanation for the extremely low incidence of awareness noted in the Pollard et al study (0.007%) might be that patients were not asked as directly about awareness as they were in other studies. They note that other studies have found that patients may not choose to discuss or recall that they were aware unless they are asked directly about it on more than one occasion. Given the potential impact this variable has on the cost-effectiveness we hope that the Committee will consider this possible explanation carefully.	
3	72.	168	Table 97	The scenario analysis considering the utility decrement for PTSD also reinforces the potential value of Entropy for high risk patients and the consistency of the results across a range of input possibilities.	
2	73.	pp. 170 – 186	Narcotrend compared with Standard clinical monitoring	We wish to reiterate that, absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	

National Institute for Health and Clinical Excellence

Depth of anaesthesia monitoring (E-Entropy, Bispectral Index and Narcotrend)

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1	74.	176	Table 108	*In the table head, please write (instead of BIS):* Narcotrend	
1	75.	177	Table 109 Heading	Narcotrend *(spelling)*	
1	76.	182	Table 116	Narcotrend *(spelling, 4x)*	
1	77.	183	Table 117	Narcotrend *(spelling, 4x)*	
1	78.	184	Table 118	Narcotrend *(spelling, 6x)*	
1	79.	185	Table 119	Narcotrend *(spelling, 4x)*	
1	80.	186	Table 120	Narcotrend *(spelling, 8x)*	
1	81.	186	last	Narcotrend *(spelling)*	
2	82.	186	Cost Effectiveness Summary	*"No robust evidence was identified on the effectiveness of Entropy or Narcotrend in avoiding intraoperative awareness or POCD and, in the absence of such evidence, we have assumed that the effect estimates derived for BIS can be applied."* We wish to reiterate that, absent NICE evaluation of	

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				one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	83.	186	Cost-effectiveness summary	While the assessment group is correct that there are gaps in the evidence for Entropy around effectiveness in avoiding awareness or POCD, we feel that the assumption of equivalence to BIS is justified (see comment 55). In addition, we feel that the developed model has not given sufficient weight to other important outcomes such as PONV, time to recovery and its impact on cost etc. While, these variables may be difficult to quantify within the published literature we feel that their potential impact should be considered further. Perhaps the expert Committee members can provide some guidance as to values to include in the model for sensitivity analysis.	
3	84.	187	Cost-effectiveness summary	It is important to highlight within the summary of cost-effectiveness that for high risk patients the results of the various analyses suggest that Entropy is consistently cost-effective. This is based on a model that is heavily weighted on the effectiveness of monitors on the incidence of awareness and subsequent LPS and PTSD. As noted in comment	

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				3 we would suggest that the model does not adequately reflect the importance of other variables such as PONV, POCD and the impact they might have on associated costs. If the model could be balanced to reflect the additional impact of costs of PONV, time to recovery, cost of POCD, we feel that the results of the model will only demonstrate a consistent message in favour of Entropy being cost-effective for all patients.	
2	85.	190	Explicit intraoperative awareness, paragraph 1, p. 190	*"It is not fully clear why the results of this trial (Avidan et al) were contrary to expectation."* Avidan uses ETAC as a comparator for BIS in his study. ETAC monitoring is not standard practice, nor is it the clinical monitoring standard identified as the comparator in this evaluation (see the clinical monitoring standard, page 11, which includes tachycardia, hypertension, sweating, lacrimation, movement/grimacing, and tachypnea).	
2	86.	190	Explicit intraoperative awareness, paragraph 2, p. 190	*"In these RCTs the sample sizes ranged from 10 to 160 patients per study group, which most likely would be insufficient for detecting clinically meaningful differences in intraoperative awareness, given the low incidence of this event."* There are several references within the DAR that	

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				note the significant quantity of BIS outcomes research compared to the other technologies evaluated. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies. Scientific conclusions are more powerful with more sampling/data.	
2	87.	191	Explicit intraoperative awareness, paragraph 2, p. 191	*"...BIS monitoring is associated with reduced likelihood of explicit intraoperative awareness. However, this may not be applicable where inhaled general anaesthesia is solely used".* This conclusion is based on studies in which ETAC protocol is used as a comparator for BIS. ETAC protocol (target volatile anesthetic administration and gas monitoring) is not standard practice, nor is it the clinical monitoring standard identified as the comparator in this evaluation (see the clinical monitoring standard, page 11, which includes tachycardia, hypertension, sweating, lacrimation, movement/grimacing, and tachypnea).	
2	88.	192	Sequelae and long-term	*"None of the trials of Narcotrend were statistically powered to detect differences in anaesthetic consumption."*	

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			consequences; end of paragraph 3, p. 192	The quantity of BIS outcomes research is significantly greater than that of the other technologies evaluated. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies. Scientific conclusions are more powerful with more sampling/data.	
3	89.	194	Time to eye opening	As previously stated in comment 39 we believe that all reductions in outcomes such as this can ultimately lead to improved efficiencies in the running of the operating theatre.	
3	90.	195	Time to extubation	As previously stated in comment 39 we believe that all reductions in outcomes such as this can ultimately lead to improved efficiencies in the running of the operating theatre.	
3	91.	196	Outcomes related to PACU stay	As previously stated in comment 39 we believe that all reductions in outcomes such as this can ultimately lead to improved efficiencies in the running of the operating theatre.	
3	92.	196	Time to response to	As previously stated in comment 39 we believe that all reductions in outcomes such as this can ultimately lead to improved efficiencies in the running of the	

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			commands	operating theatre.	
3	93.	197	Time to first movement response	As previously stated in comment 39 we believe that all reductions in outcomes such as this can ultimately lead to improved efficiencies in the running of the operating theatre.	
2	94.	201	BIS compared with standard clinical monitoring; paragraph 1, p. 201.	"*The majority of the additional cost of BIS monitoring was attributable to the sensors attached to the patient (90% of additional cost, per patient).*" It should be noted that the BIS unilateral sensor is the standard for general anesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors.	
2	95.	201	BIS compared with standard clinical monitoring; paragraph 1, p. 201.	"…the cost effectiveness results were largely insensitive to including an effect of BIS on PONV…" We respectfully disagree. If the fully burdened cost of treating PONV is included, the impact would be greater. See above comment on the cost to treat PONV from Liu (Anesthesiology 2004)	

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2	96.	203	Entropy compared with standard clinical monitoring, paragraph 2, p. 203	"*In the absence of evidence specific to Entropy we have applied the effectiveness estimates derived for BIS, described above. This meant that the modelled clinical effectiveness of Entropy was identical to that reported for BIS – this is an untested assumption and must be considered a weakness in the evidence base for Entropy."* We wish to reiterate that, absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
2	97.	203	Entropy compared with standard clinical monitoring, paragraph 4, p. 203	*"The additional cost of Entropy monitoring was approximately half that of BIS monitoring, with the majority being attributable to the sensors attached to the patient (80% of additional cost per patient). Entropy monitoring was associated with improved outcomes, based on applying clinical effectiveness evidence reported for BIS."* Here we wish to reiterate two points: 1. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the	

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				E-Entropy and Narcotrend technologies; and 2. The BIS unilateral sensor is the standard for general anesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors.	
3	98.	203	Entropy	In the absence of evidence on Entropy we believe that the assumption of equivalence to BIS is justified (see comment 15).	
2	99.	205	Narcotrend compared with standard clinical monitoring, paragraph 2	"*In the absence of evidence specific to Narcotrend we have applied the effectiveness estimates derived for BIS, described above. This meant that the modelled clinical effectiveness of Narcotrend was identical to that reported for BIS – this is an untested assumption and must be considered a weakness in the evidence base for Narcotrend."* We wish to reiterate that, Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	

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2	100.	206	Narcotrend compared with standard clinical monitoring, paragraph 1, p. 206.	*"The additional cost of Narcotrend monitoring was approximately half that of Entropy monitoring, and approximately a quarter that of BIS – primarily due to differences in the cost of the sensors attached to the patient. In contrast to BIS and Entropy the majority of the additional cost of Narcotrend monitoring was attributable to the monitor (90% of additional cost per patient) rather than the sensors. Narcotrend monitoring was associated with improved outcomes, based on applying clinical effectiveness evidence reported for BIS."* With all due respect: *Narcotrend monitoring was associated with improved outcomes, based on applying clinical effectiveness evidence reported for BIS* - this statement just cannot exist within this document. If Narcotrend was capable of improving outcomes, there would be evidence for it. To apply the specific clinical evidence for the BIS technology to the Narcotrend technology is an un-guided leap of faith and conjecture. Here we again wish to reiterate two points: 1. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the	

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				E-Entropy and Narcotrend technologies; and 2. The BIS unilateral sensor is the standard for general anesthesia monitoring. Bilateral sensors are indicated only for specific patient subgroups and approximate 15% of usage. We suggest calculation of a weighted average for the cost of BIS sensors.	
2	101.	206	Narcotrend compared with standard clinical monitoring, paragraph 2, p. 206.	*"...given that Narcotrend was associated with improved outcomes and reduced costs it dominated standard clinical monitoring."* We wish to reiterate that, absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
2	102.	208	Strengths and limitations of the assessment, paragraph 1, p. 208	The reference to the Liu (2004) systematic review and meta-analysis is a strength not previously referenced in the DAR. This study found BIS-guided anaesthetic delivery to significantly reduce anaesthetic consumption, PONV and time spent in the PACU. We suggest that this systematic review and meta-analysis should be more carefully considered in the analysis.	

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2	103.	208	Strengths and limitations of the assessment, paragraph 1, p. 208	*"A disadvantage of our pragmatic approach is that we have not presented full details of those BIS trials included in the Cochrane review.....no systematic reviews of Entropy-guided anaesthesia or Narcotrend-guided anaesthesia appear to have been published...."* We wish to reiterate that, Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
3	104.	208	7.2	While we acknowledge the strength of evidence provided within RCTs it would be good to know if the assessment group also considered other study designs. It is feasible to have badly designed RCTs which add little value to the discussion, while well designed observational or registry type data can add much to discussions.	
2	105.	209	Strengths and limitations of the assessment, paragraph 1,	[Discussing Entropy & Narcotrend] – *"The primary studies also predominantly reported secondary outcomes which were often based on relatively small sample sizes, with unknown statistical validity."* There are several references within the DAR that	

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			p. 209	note the significant quantity of BIS outcomes research compared to the other technologies evaluated. Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies. Scientific conclusions are more powerful with more sampling/data.	
2	106.	210	Strengths and limitations of the assessment, paragraph 1, p. 210	"*In particular no evidence on the effectiveness of Entropy and Narcotrend on the incidence of intraoperative awareness was identified.....effectiveness evidence for BIS can be applied to both Entropy and Narcotrend. These are untested assumptions and must be considered a weakness in the cost effectiveness evidence base....Evidence on the effectiveness of any depth of anaesthesia monitoring on POCD is also limited to BIS...we have assumed that evidence for BIS can also be applied to Entropy and Narcotrend – again this is an untested assumption."* There are several references within the DAR that note the significant quantity of BIS outcomes research compared to the other technologies evaluated. Absent NICE evaluation of one technology to another for efficacy, we question the	

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				extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies. Scientific conclusions are more powerful with more sampling/data.	
3	107.	210	7.2	We would argue that the trigger for PTSD is not necessarily relevant to this discussion on impact on QoL associated with PTSD. In a paper by McCrone, Knapp and Cawkill (2003) Posttraumatic stress disorder (PTSD) in the armed forces: health economic considerations. LSI research online: http://eprints.lse.ac.uk/archive/00000329, it was noted that combat PTSD is not a disorder in itself and PTSD that follows other events may be no less serious.	
3	108.	211	7.3	It was good to see that the assessment group did look for non-RCT studies that might indicate the effectiveness of modules on awareness. Can they also confirm if they considered other non-RCT studies for baseline incidence of awareness which is the other critical variable in the model, or any of other variables such as PONV, etc.	
1	109.	212	1	*1. The Narcotrend monitor does not use the NarcoWin software for recording, analysis, and classification of EEGs. NarcoWin is a software that*	

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				can be used for reanalysing already existing Narcotrend EEG recordings and is run on Windows PCs. *2. The Narcotrend module is not an upgrade of the Narcotrend-Compact M, but a parallel development. Therefore, please delete the sentence:* *"Also the Narcotrend-Compact M monitor which used the NarcoWin software seems to have been upgraded to the NarcoWin module."*	
3	110.	214	8	There is again note of clinically modest impact of some of the outcomes. We would ask that serious consideration be given to the potential impact of such outcomes as time to recovery from the perspective of efficiency and potential costs (please see comment 12).	
3	111.	214	8	Surely overall, BIS is associated with a statistically significant reduction in intraoperative awareness as demonstrated in Figure 2, page 60.	
2	112.	214	Conclusions	*"Overall, BIS was not associated with statistically significant reduction in intraoperative awareness in patients classified as at higher risk..."* This sentence appears to have an error based upon	

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				the DAR assessment. See Table 40: Pooled effect in High Risk Patients in 7 trials has a Peto Odds ratio of 0.45 (0.25-0.81). Thus the conclusion should state: Overall, BIS was associated with statistically significant reduction in intraoperative awareness in patients classified as at higher risks. This conclusion would be enhanced by a clear statement, that unlike BIS, no evidence exists regarding the ability of E-Entropy or Narcotrend to impact intraoperative awareness.	
3	113.	215	8 Suggested research priorities	We would suggest that while the evidence base is still limited there is sufficient RCT evidence in some large sample sizes to demonstrate the potential of depth of anaesthesia monitors. The on-going RCTs will hopefully add positively to this evidence base to confirm the clinical and cost-effectiveness of these monitors. GE is sponsoring an international multicentre RCT on surgical plethysmography index (SPI) when used together with Entropy, starting late 2012. The assumption is that SPI and Entropy yields improved targeted titration of anaesthetics on opioids. This may result in reduced awareness, PONV, and faster discharge both from OR and PACU. Further	

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				information on this study is available upon request.	
2	114.	216	Suggested research priorities, paragraph 2	*"The data from current E-Entropy and Narcotrend RCTs are inadequate to statistically pool quantitative effect estimates for relevant outcomes."* Absent NICE evaluation of one technology to another for efficacy, we question the extrapolation of BIS-specific clinical and economic conclusions to the E-Entropy and Narcotrend technologies.	
1	115.			**Remarks** For the selection of articles relevant for the assessment of depth of anaesthesia monitors it was necessary to define clear and strict criteria. So, articles not meeting the criteria, as non-English articles, could not be included. Articles, further to the selected ones, and the clinical practice show that EEG monitoring during anaesthesia allows age-adjusted dosing, gender-adjusted dosing, dosing of hypnotics adjusted to the opioid doses, detection of epileptiform EEG activity, especially during sevoflurane anaesthesia, and detection of hypoxic episodes.	

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				For example, a multicentre analysis (Klin Neurophysiol 2010; 41: 28-32) including 3,542 patients showed that EEG monitoring influences the dosing practice of propofol, taking into account age, gender, mode of propofol administration, and opioid choice. Without EEG monitoring, nearly every fifth patient was overdosed and in about every 17th patient anaesthesia was very light with a high risk of awareness. EEG monitoring caused a significant reduction in propofol consumption with TCI (target-controlled infusion). This analysis confirms the high interindividual variability of the drug requirements during anaesthesia.	