ABSTRACT

Introduction The use of Bispectral Index (BIS) monitors for assessing depth of sedation has led to a reduction in both the incidence of awareness and anaesthetic consumption in total intravenous anaesthesia. However, these monitors are vulnerable to artefacts. In addition to the processed number, the raw frontal electroencephalogram (EEG) can be displayed as a curve on the same monitor. Anaesthesia practitioners can learn to interpret the EEG in a short tutorial and may be quicker and more accurate than BIS in assessing anaesthesia depth by recognising EEG patterns. We hypothesise that quality of recovery (QoR) in patients undergoing laparoscopic surgery is better, if propofol is titrated by anaesthesia practitioners able to interpret the EEG.

Methods and analysis This is a multicentre, double-blind (patients and outcome assessors) randomised controlled trial taking place in four Swiss hospitals. Patients aged 18 years or older undergoing laparoscopic procedures with general anaesthesia using propofol and anaesthesia practitioners with more than 2 years experience will be eligible. The primary study outcome is the difference in QoR 24 hours after surgery. Secondary outcomes are propofol consumption, incidence of postoperative nausea and vomiting (PONV) and postoperative delirium. QoR and propofol consumption are compared between both groups using a two-sample t-test. Fisher's exact test is used to compare the incidences of PONV and delirium. A total of 200 anaesthesia practitioners (and 200 patients) are required to have an 80% chance of detecting the minimum relevant difference for the QoR-15 as significant at the 5% level assuming a SD of 20.

STRENGTH AND LIMITATIONS OF THIS STUDY

⇒ Multicentre, randomised, double-blind (patients and outcome assessors) intervention study comparing the use of a tutorial on the interpretation of electroencephalogram curve waveforms versus standard monitoring including Bispectral Index monitoring regarding quality of recovery (QoR) of surgical patients.

⇒ Overall QoR as the primary endpoint combines and reflects patient-centred perioperative outcomes.

⇒ The QoR Scores have been extensively tested and show excellent test-retest reliability, discriminative abilities and responsiveness to changes.

⇒ As a first secondary outcome, we aim to compare propofol consumption, which is closely associated with time to extubation and duration of stay in the postanaesthesia care unit.

⇒ The results and conclusions of this trial are limited to intravenous anaesthesia with propofol target-controlled infusion and to procedures of similar complexity.

Ethics and dissemination Ethical approval has been obtained from all responsible ethics committees (lead committee: Ethikkommission Nordwest- und Zentralschweiz, 16 January 2021). The findings of the trial will be published in a peer-reviewed journal, presented at international conferences, and may lead to a change in titrating propofol in clinical practice.

Trial registration number www.clinicaltrials.gov: NCT04105660
INTRODUCTION
Background
In daily clinical practice, Bispectral Index (BIS) monitoring is widely used in addition to standard clinical monitoring to assess the depth of sedation during general anaesthesia. These monitors transform the frontal electroencephalogram (EEG) of a patient into a number between 0 (isoelectric EEG) and 100 (fully awake) using a mathematical algorithm. This index can be used to titrate anaesthetics to the desired depth of anaesthesia. The use of such processed EEG (pEEG) monitors in addition to standard clinical monitoring for assessing depth of sedation has been shown to reduce anaesthetic consumption and incidence of awareness, as well as shorten the time to extubation and time spent in the postanaesthesia care unit (PACU) if intravenous anaesthetics are administered. Recent studies have shown that a BIS-guided anaesthesia can even decrease the risk of postoperative delirium, postoperative cognitive dysfunction and postoperative nausea and vomiting (PONV) after general anaesthesia. However, controversy remains about the latter topics, and the mechanism explaining these associations has yet to be determined.

As with any monitor, the processed numerical output of the BIS monitor is vulnerable to artefacts and is often misleading, especially if it is not interpreted within the clinical context. It is apparent that the complexity of neuropsycharmacology and neurophysiology will occasionally influence pEEG. But in addition to the processed numerical output, the BIS monitor can also display the raw frontal EEG curve. Many of the factors that can mislead the pEEG can be readily identified by scrutinising the raw frontal EEG. However, in general the raw EEG curve is not systematically used in daily clinical practice. Barnard et al have shown that anaesthetists can recognise anaesthesia-related raw EEG patterns after taking a short tutorial and are potentially even faster in recognising the clinically relevant patterns than calculated BIS values. The effectiveness of this teaching method has been confirmed by Bottros et al. Recently, a different learning curriculum on EEG spectrogram interpretation has been shown to increase residents’ knowledge about EEG.

Rationale and evidence gap
As interindividual variability in the effect-site concentrations of the intravenous anaesthetic propofol to induce and maintain anaesthesia is high, it is important to be able to titrate propofol to the optimal individual level to avoid complications of underdosage and overdosage. If not enough anaesthetic is delivered, the patient can remain conscious during surgery, causing trauma, anxiety and vomiting, and harbours the risk of awareness. Evidence for a harmful effect of too deep general anaesthesia measured by low BIS values has thus far been based on large observational studies where a possible association between depth of anaesthesia and increasing morbidity and mortality has been seen. A definitive conclusion about the true causality between increasing depth of general anaesthesia and postoperative mortality remains unclear despite the landmark trial by Short et al.

To the best of our knowledge, the added value of the interpretation of the raw frontal EEG to the processed BIS and its clinical relevance in assessing depth of anaesthesia and for titrating anaesthetics have never been investigated. Although the raw frontal EEG curve can be displayed on the same monitor, it is generally not systematically used for titrating propofol in daily clinical practice. As anaesthesia practitioners can be trained to read and interpret the unprocessed EEG, they may be able to assess depth of anaesthesia quicker and more accurately than anaesthesiologists relying on processed BIS values alone. This may refine the titration of propofol, minimise side effects and improve the quality of recovery (QoR) of patients after general anaesthesia.

METHODS AND ANALYSIS
Study design
This multicentre, randomised, double-blind, intervention trial compares the QoR from propofol anaesthesia in patients undergoing laparoscopic surgery of a minimal duration of 60 min under general anaesthesia in two patient groups. Patients in the intervention group will be anaesthetised by anaesthesia practitioners using the raw frontal EEG curve in addition to BIS and standard clinical monitoring to assess depth of anaesthesia after having completed a teaching module about the interpretation of EEG waveform patterns. The control group of patients will be anaesthetised by anaesthesia practitioners using standard clinical monitoring including BIS to assess depth of anaesthesia. As soon as the anaesthesia practitioner is assigned to a study patient, they will be randomised to one of the two treatment arms.

Study sites
The study will allocate patients to anaesthesia practitioners at one of the four Swiss study centres, University Hospital Basel, Basel; Kantonsspital Graubünden, Chur; Kantonsspital Aarau, Aarau; and Geneva University Hospitals, Geneva.

Anaesthesia practitioners’ selection and recruitment
Anaesthesia practitioners will be informed and recruited from the hospitals’ staff. The informed consent form clearly states that there would be no adverse consequences for anaesthesia practitioners who choose not to participate.

Randomisation and blinding
Anaesthesia practitioners will be assigned to anaesthetise one of the eligible consenting patients and will be randomly allocated into two groups. Randomisation for a 1:1 allocation of the study treatment is provided through an online randomiser to ensure allocation concealment. This online randomiser is integrated into...
the password-protected database. Randomisation will take place 1 week to 1 day before surgery after having controlled the inclusion and exclusion criteria. The randomisation list has been generated in Intercooled Stata V.16.1 (StataCorp, College Station, Texas, USA), stratified according to the trial centre with variable block sizes between 6 and 10. The list is safely stored in a separate and sealed file, which will only be opened if unblinding becomes necessary. This is considered to be unlikely since standard clinical monitoring including BIS monitoring will be maintained. Patients and outcome assessors will be blinded to the treatment arm. In addition, the statistician will remain blinded to group allocation until the data are analysed.

**Intervention**

In the intervention group, anaesthesia practitioners will learn about the interpretation of frontal EEG waveform patterns in a 15 min tutorial, followed by a test involving interpretation of EEG segments and self-assessment (another 15 min), which was kindly provided to us for this randomised controlled trial (RCT) by Barnard et al. The design of the original tutorial has been slightly modified from its original version to resemble the EEG tracing on the BIS monitor. Furthermore, we added four clinical examples to the tutorial. In these examples the BIS value and the raw EEG in the context of a specific clinical situation is presented to participants and they have to decide if and how to adapt the target site concentration of propofol. An explanatory answer is presented to the participants for each case. So, there is advice how to deal with four specific situations, but not for other situations. Participants are not supposed to disregard the BIS value completely but to use information from the raw EEG curve in addition to the BIS value or to ‘overrule’ the BIS value in certain situations. For those with limited understanding of English, the written and spoken text of the tutorial has been translated into French and German. The participating anaesthesia practitioners in the intervention group will receive online access to the tutorial and the test including self-assessment for self-study. It is up to the anaesthesia practitioners to decide how often they complete the training; they are permitted to redo any part of the tutorial. Immediately after the tutorial, the anaesthesia practitioners will complete a self-assessment on their ability to match sample EEGs with behavioural states (also 15 min long) for self-study, followed by four clinical examples. They are advised to use their new knowledge about the raw frontal EEG in addition to the BIS values to titrate the anaesthesia depth. As BIS monitoring is standard of care during intravenous anaesthesia in the participating institutions, blinding to BIS was not possible for participants in this kind of study. However, patients and outcome assessors were blinded to BIS monitoring and group allocation. In the control group, the participating anaesthesia practitioners will not receive training in the interpretation of EEG and anaesthesia-associated changes and will not be allowed to display the raw frontal EEG on the anaesthesia monitor. The following day (or within a week at the most), the anaesthesia practitioners in both groups will titrate the propofol dose during general anaesthesia in their allocated patient. The trial flow chart can be seen in figure 1.

All patients will receive intravenous anaesthesia with propofol target-controlled infusion based on the Schnider model. BIS monitoring (dominant hemisphere; BIS Quatro, Covidien, Medtronic (Schweiz), Münchenbuchsee) will be used in addition to standard clinical monitoring (pulse oximetry, ECG, blood pressure and end tidal concentration of carbon dioxide). In the control group, only BIS (but not the raw frontal EEG curve) and clinical parameters will be available for assessing depth of anaesthesia and titration of propofol. The proposed intraoperative dosing scheme for propofol and opioids can be seen in figure 2. In the intervention group, the raw frontal EEG curve will be displayed for reference in addition to BIS and the clinical parameters for assessing the depth of anaesthesia.

Fentanyl dose will be limited to a maximum of 5 µg/kg body weight and remifentanil to a target effect site concentration of 5 ng/mL. The anaesthesia practitioners will administer anaesthesia uninterrupted from induction to emergence. Paracetamol 1 g, ketorolac 30 mg, clonidine 150 µg and lidocaine up to 1.5 mg/kg body weight are allowed as additional intraoperative analgesics. Other hypnotics than propofol, such as ketamine or midazolam preoperatively or intraoperatively are not allowed as they can affect BIS. Postoperative analgesia will consist of a combination of metamizole, paracetamol, non-steroidal anti-inflammatory drugs, and intravenous or oral clonidine and opioids. We know that different analgesic regimens may influence QoR, however we refrained from more standardised analgesic regimens as individual dosing of postoperative analgesics may better address individual analgesic needs of patients after different operations. Dexamethasone 4 mg and serotonin antagonists will be routinely used as intraoperative PONV prophylaxis. For treatment of PONV, dimenhydrinate or droperidol can be administered additionally at the discretion of the treating anaesthesiologist.

After the end of the study period, the EEG-training tutorial will also be offered to anaesthesia practitioners in the control group.

**Inclusion criteria**

Anaesthesia practitioners (randomisation and intervention unit) must have a minimum of 2 years training in anaesthesiology. This means that anaesthesia residents must be at least in their third year of anaesthesiology training and anaesthesia nurses must be certified.

Patients aged 18 years or older with an American Society of Anaesthesiology (ASA) physical status I–IV undergoing planned in-hospital laparoscopic surgery with general anaesthesia using propofol are eligible for inclusion. As QoR-15 has been shown to be higher in patients recovering from less complex procedures, eligible surgical
Open access

Anaesthesia practitioners (participants) and patients: recruitment and informed consent

Stratified randomisation according to centre

Day -7 to -1 Training for participants in interpretation of EEG waveforms

Day 0 Patients undergoing laparoscopic surgery with general anaesthesia including clinical standard, BIS and EEG monitoring

Day 0 Patients undergoing laparoscopic surgery with general anaesthesia including clinical standard and BIS monitoring

Day 0 Follow-up on day of surgery before discharge from PACU

Day 0 Postoperative follow-up on ward on day of surgery

Day 1 until discharge Daily follow-up until hospital discharge

Primary outcome:
• QoR-15 scale 24 hours after surgery

Secondary outcomes:
• Propofol consumption
• QoR-15 scale 48 hours after surgery
• Burst suppression ratio
• Total amount of vasoactive drugs
• Time to extubation
• Time spent in PACU

• Aldrete score at discharge from PACU
• Incidence of postoperative delirium
• Incidence of PONV
• Risk of awareness
• Length of hospital stay
• Pain

Figure 1 Trial flow chart. BIS, Bispectral Index; EEG, electroencephalogram; PACU, postanaesthesia care unit; PONV, postoperative nausea and vomiting; QoR, quality of recovery.

Figure 2 Intraoperative dosing scheme for propofol and opioids. BIS, Bispectral Index.

procedures will be restricted to a limited number of procedures of similar complexity, according to the British United Provident Association (BUPA) classification (all of major or major + complexity). Eligible surgical procedures include laparoscopic hernia repairs (intrapерitoneal inlay mesh, transabdominal preperitoneal and total extraperitoneal hernia repair), laparoscopic cholecystectomies and hysterectomies, or other diagnostic and interventional gynaecological or abdominal surgery procedures with a minimal duration of surgery of 60 min.

Exclusion criteria
Previous participation in this trial is an exclusion criterion for anaesthesia practitioners and patients. Same-day surgical patients, patients <18 years of age, pregnant women, patients with an allergy to propofol or a language barrier, patients with a known brain
pathology such as seizure disorders, dementia, cerebrovascular disease, brain death or who are administered hypnotics other than propofol, such as ketamine or midazolam preoperatively or intraoperatively, will be excluded as all of these conditions or medications can affect the raw EEG waveform and, correspondingly, the BIS values.

Sample size
In the study by Myles et al,\(^47\) the minimum clinically important difference for QoR-15 (range 0–150) was 8, with a mean score of 112 (SD 19) about 24 hours and 122 (SD 17) about 48 hours after surgery. A total of 200 anaesthesia practitioners (and 200 patients) are required to have an 80% chance of detecting a difference of 8 points in the QoR-15 Scale as significant at the 5% level, assuming an SD of 20. The effect size is based on the minimum relevant difference as derived by Myles et al,\(^47\) as this difference should be reached to claim the interpretation of the raw EEG as an added value over BIS monitoring alone. In order to allow for a greater heterogeneity, we increased the SD of 17 or 19 observed in the study from Myles et al\(^47\) to 20.

This sample size would also allow detecting a 0.4 mg/kg/hour decrease in propofol consumption (secondary end point) as significant at the 5% level assuming an SD of 1 mg/kg/hour and a power of 80%. This effect size was derived by assuming about half of the effect size achieved by adding BIS monitoring to the standard clinical monitoring. The SD was derived from the trials using propofol summarised in the latest Cochrane Review.\(^19\)

Patient and public involvement
Patients were involved in determining primary and secondary outcomes of this trial as we asked 61 patients about what they consider to be the most important outcome after general anaesthesia concerning their own postoperative course (EKNZ BASEC Nr Req-2019-00132). Intraoperative awareness, postoperative pain, PONV, minimal drug dosage and fast recovery, ranked in this order, were the five most common endpoints according to the patients’ opinions. As the sample size for incidence of awareness or PONV would exceed feasibility to conduct this trial, we decided to focus on an overall QoR measure as our primary endpoint. QoR combines and reflects all of these patient-reported important outcomes, including pain.

Potential participants will be identified and recruited during assessment in the preoperative anaesthesia clinic 1 day to several days before the scheduled intervention, allowing adequate time to obtain informed consent. However, patients are not involved in recruitment or conduct of the study. The burden of the intervention was not assessed by patients themselves, however this aspect can be addressed by patients during follow-up visits on postoperative days 1 and 2.

Primary outcome
The primary endpoint is QoR on the first postoperative day according to the QoR-15 Scale.\(^45\) This crucial patient-reported perioperative outcome is one of the main targets pursued in this study.

The QoR Score QoR-40 was developed by a research group in Australia, which focused on the standardised use of patient-centred perioperative outcomes in consideration of the patient’s point of view.\(^49\)\(^50\) It has been tested extensively and shows excellent test-retest reliability, discriminative abilities and responsiveness to change.\(^49\)\(^50\) We chose to use the QoR-15 Scale (ie, the short form of the QoR-40 Scale) for measurement as it still preserves the five dimensions of health: patient support, comfort, emotions, physical independence and pain, but is more feasible and showed good scaling properties consistent with a normal distribution.\(^48\)\(^51\) For an even shorter form of the same instrument, the QoR-9, a cross-cultural adaptation was done for a German translation showing properties similar to the original English version.\(^52\)\(^53\) Furthermore, QoR-15 was translated into German by a German native speaker and back-translated into English by an English native speaker.\(^53\) In the meantime, a validated French translation of QoR-15 has been published.\(^54\)

Secondary outcomes
The secondary outcomes include anaesthetic consumption, common side effects of anaesthesia and standardised markers for a qualitative good recovery after anaesthesia to capture a detailed range of plausible harms or benefits of the additional interpretation of the raw frontal EEG to BIS to assess depth of anaesthesia. The aim of these secondary outcomes is to search for consistency in results with the primary endpoint. A formal sample size calculation has only been performed for propofol consumption, for which the planned sample size allows for enough power to detect a relevant difference.

1. Propofol consumption in mg/kg/hour
2. Time to extubation
3. QoR-15 Scale 48 hours after surgery
4. Incidence of postoperative delirium (assessed by the Confusion Assessment Method (CAM))\(^55\) on postoperative days 1 and 2
5. Incidence of PONV (nausea and vomiting considered separately) in PACU, at discharge from PACU and on postoperative days 1 and 2.

Exploratory outcomes
We aim to investigate descriptively a number of further exploratory endpoints to gain supportive, mechanistic information. We also look for consistency with the primary and the secondary end points.

1. Total amount and type of vasoactive drugs used intraoperatively
2. Duration of BIS <30 and average burst suppression ratio (in the intervention arm only, assessed every 10 min intraoperatively)
3. Time spent in the PACU
4. Pain measured on a Visual Analogue Scale from 0 to 10
5. Discharge readiness according to the Aldrete Score
6. Risk of awareness according to the Brice interview
7. Length of hospital stay.

**Statistical analysis**

The QoR-15 Scale will be compared between both groups using a two-sample t-test and a linear regression model additionally adjusting for the stratification variable trial centre. Propofol consumption will also be compared between both groups using a two-sample t-test as well as a linear regression model additionally adjusting for the stratification variable. Kaplan-Meier curves as well as a Cox-proportional hazards model will be applied for comparing the time to event end points (time to extubation, time to discharge from PACU and time to fit for discharge) between both groups. Fisher’s exact test will be used to compare the incidences of PONV and delirium. Secondary end points other than propofol consumption will only be analysed descriptively or using graphs.

Dropouts, if any, will be replaced by recruitment of new subjects in order to reach the planned sample size of 200 anaesthesia practitioners and patients. A sensitivity analysis will be performed by imputing missing values using multiple imputations if the percentage of missing data in important variables exceeds 10%. A further sensitivity analysis will be performed by adjusting for potential chance confounding by baseline factors despite the randomised design. These factors include patient age, comorbidities (ie, ASA class), complexity of the surgical procedure (according to BUPA), fentanyl dose intraoperatively as well as the profession and the experience of the anaesthesia practitioners delivering anaesthesia.

We will follow the Consolidated Standards of Reporting Trials guidelines for reporting RCTs. Analyses will be performed using Intercooled Stata V.16 (StataCorp, College Station, Texas, USA).

**Collection of data**

All patients will be followed on postoperative days 1 and 2 by an independent study team member blinded to patients’ group allocation. Afterwards, patient records will be searched for serious adverse events (SAEs) until hospital discharge. Blinded study team members will collect data to describe and measure all predefined outcomes. All variables, which are routinely collected and recorded, will be entered directly into the study-specific internet-based database, as the anaesthesia protocol or the discharge letter are electronically available for data verification. In addition, baseline data (demographic details and medical history) will be collected and entered in the database. For study-specific endpoints, which are not routinely collected, a paper-based case report form will be completed and transferred into the electronic database. The following data are study-specific: QoR-15 Scale, CAM and Brice interview. In case of an SAE, both investigator and sponsor investigator will make a causality assessment of the event to the trial intervention. All SAEs will be documented immediately (within a maximum of 24 hours) to the sponsor investigator of the study and reported to the ethics committee if it cannot be excluded that the SAE is attributable to the intervention under investigation. All patients will be followed up until hospital discharge. Recruitment started on 1 July 2021. Currently, patients and anaesthesia practitioners are recruited at three centres while the fourth centre will be starting recruitment in the next few months. As of 1 November 2021, 90 anaesthesia practitioners have been randomly allocated to eligible patients and data have been collected. During this period, nine patients have been excluded after randomisation. Of these, four patients underwent an unplanned open procedure, four patients had duration of surgery of less than 1 hour and one patient had unplanned ambulatory treatment after surgery. Reasons for not including patients were: allocated anaesthesia practitioner unavailable to anaesthetise the patient on the day of the procedure or postponement of the planned procedure. Due to high acceptance for clinical research in the participating hospitals, recruitment of participants and patients is currently exceeding the target recruitment rate (figure 3).

**Data monitoring**

Monitoring will be performed at each centre by a qualified person who is independent of the research team. The source data/documents will be accessible to monitors and questions are answered during monitoring. Site visits are scheduled before enrolment of the first patient, after enrolling 30 patients and after enrolment of the last patient at every study centre.

**Data availability statement**

Deidentified participant data will be available upon reasonable request from the last authors of this publication (CSB, ORCID 0000-0002-9288-117X and SD-K, ORCID 0000-0001-7219-7138).
This clinical trial entailing only minimal risks falls under Category A according to ClinO, Art. 61 and has been approved by the ethics committees of all four trial centres (Lead ethics committee Ethikkommission Nordwest- und Zentralschweiz, EKNZ 2019-01857, Commission Cantonale d’éthique de la recherche Genève, Kantonale Ethikkommission Zürich).

For details concerning trial registration see online supplemental file 1. The study has been registered on www.clinicaltrials.gov (NCT04105660). The study intervention consists of additional display and interpretation of EEG waveforms in addition to the standard monitoring including BIS alone to titrate propofol. As standard monitoring with BIS will be available in both groups, patients are not at increased risk for underdosage of propofol. The results of the study will be published in a peer-reviewed journal and presented at national and international conferences. Furthermore, results may lead to a change in titrating propofol in clinical practice. If we can demonstrate better QoR from general anaesthesia when raw frontal EEG is interpreted systematically in patients, follow-up studies would be needed to confirm our results before patient organisations could be involved and informed about how improvement of patients’ recovery after total intravenous recovery can be achieved. We plan to analyse the educational aspect of the kind of tutorial we used in this study in a follow-up study, the results of which will be published in a medical education journal.

Contributors BUG has made a substantial contribution to planning, design and development of the study protocol. She drafted the article and approved the version to be published. VG is involved in patient recruitment and follow-up. She critically revised the article for important intellectual content, and approved of the final version to be published. UK is involved in patient recruitment and follow-up. He critically revised the article for important intellectual content, and approved of the final version to be published. SF is involved in patient recruitment and follow-up. He critically revised the article for important intellectual content and approved of the final version to be published. SD-K has made a substantial contribution to the concept and design of the study protocol; she is co-principal investigator of the study and raised third-party funding; she is involved in patient and anaesthesia practitioner recruitment. She critically revised the article for important intellectual content and approved the final version to be published. CSB has made a substantial contribution to the concept and design of the study protocol; he is co-principal investigator of the study and raised funding; he is involved in patient and anaesthesia practitioner recruitment. He critically revised the article for important intellectual content and approved the version to be published.

Funding This research received grants from the Swiss Life Jubiläumsstiftung, from the Foundation for Research and Education, University Basel, and from the Foundation for Research and Education in Anaesthesia, Basel. In addition, the project has been accepted to be listed in the portfolio for fundraising by the patient Research Foundation, University Hospital Basel.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. All data relevant to the study are included in the article or uploaded as supplementary information. Data will be available from the corresponding author after analysis, or from a data deposit. This is mentioned in the study protocol approved by the ethics committee.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD Christoph S Burkhardt http://orcid.org/0000-0002-9288-117X

REFERENCES

1. Liu J, Singh H, White PF. Electroencephalographic bispectral index correlates with intraoperative recall and depth of propofol-induced sedation. Anaesth Analg 1997;84:185–9.
2. Chihiholm CJ, Zurica J, Mironov D, et al. Comparison of electrophysiologic monitors with clinical assessment of level of sedation. Mayo Clin Proc 2006;81:46–52.
3. Mathur S, Patel J, Goldstein S, StatPears treasure island (FL): StatPearls publishing copyright ©. In: Bispectral index. StatPears Publishing LLC, 2021.
4. Leslie K, Myles PS, Forbes A, et al. Recovery from bispectral index-guided anaesthesia in a large randomized controlled trial of patients at high risk of awareness. Anaesth Intensive Care 2005;33:443–51.
5. Tirén C, Anderson RE, Barr G, et al. Clinical comparison of three different anaesthetic depth monitors during cardiopulmonary bypass. Anaesthesia 2005;60:189–93.
6. Anderson RE, Barr G, Ovall A, et al. Entropy during propofol hypnosis, including an episode of wakefulness. Anaesthesia 2004;59:52–6.
7. Ellerkammern RK, Kreuer S, Wilhelm W, et al. The correlation of the bispectral index with propofol effect site concentrations is not altered by anechocohs indicated as artefact-loaded by narcotrend. J Clin Monit Comput 2004;18:583–7.
8. Ellerkammern RK, Liermann VM, Alves TM, et al. Spectral entropy and bispectral index as measures of the electroencephalographic effects of sevoflurane. Anaesthesiology 2004;101:1275–82.
9. Gao WW, He YH, Liu L, et al. Bis monitoring on intraoperative awareness: a meta-analysis. Curr Med Sci 2018;38:349–53.
Punjasawadwong Y, Phongchiewboon A, Bunchungmongkol N. Bispectral index for improving anaesthetic delivery and postoperative recovery. Cochrane Database Syst Rev 2016;6:CD003843.

Vakkaru A, Yi-Hankala A, Sandin R, et al. Spectral entropy monitoring is associated with reduced propofol use and faster emergence in propofol-nitrous oxide-alfentanil anesthesia. Anesthesiology 2005;103:274–9.

Gan TJ, Glass PS, Windsor A, et al. Bispectral index monitoring allows faster emergence and improved recovery from propofol, alfentanil, and nitrous oxide anesthesia. bis utility study group. Anesthesiology 1997;87:808–15.

McKay IDH, Voss LJ, Sleigh JW, et al. Pharmacokinetic-Pharmacodynamic modeling the hypnotic effect of sevoflurane using the spectral entropy of the electroencephalogram. Anesth Analg 2005;106:1029–1033.

Johansen JW. Update on bispectral index monitoring. Best Pract Res Clin Anaesthesiol 2006;20:81–99.

Zhang C, Xu L, Ma Y-Q. Bispectral index monitoring prevent awareness during total intravenous anaesthesia: a prospective, randomized, double-blinded, multi-center controlled trial. Chin Med J 2011;124:3664–9.

Liu SS. Effects of bispectral index monitoring on ambulatory surgery. Anesthesiology 2005;103:274–9.

Bottros MM, Palanca BJA, Mashour GA, et al. Electroencephalogram? comparison of performance with the bis and spectral entropy. Br J Anaesth 2005;94:265–66.

Ranta SO, Laurila R, Saario J, et al. Awareness with recall during general anesthesia: incidence and risk factors. Anesth Analg 1998;86:1084–9.

Lindholm M-L, Träf S, Granath F, et al. Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. Anesth Analg 2009;108:508–12.

Sessler DI, Sigl JC, Kelley SD, et al. Hospital stay and mortality are increased in patients having a “triple low” of low blood pressure, low bispectral index, and low minimum alveolar concentration of volatile anesthesia. Anesthesiology 2012;116:1195–203.

Maheshwari A, McCormick PJ, Sessler DI, et al. Prolonged concurrent hypotension and low bispectral index (‘double low’) are associated with mortality, serious complications, and prolonged hospitalization after cardiac surgery. Br J Anaesth 2017;118:40–9.

Yoon S, Yoo S, Hur M, et al. The cumulative duration of bispectral index less than 40 concurrent with hypotension is associated with 90-day postoperative mortality: a retrospective study. BMC Anesthesiol 2020;20:39–1–21.

Galley HF, Webster NR. Deep anaesthesia and poor outcomes: the jury is still out. Lancet 2019;394:1891–2.

Dell-Kuster S, Steiner LA, Chapelle C, et al. Deep anaesthesia and postoperative delirium: is the matter resolved? Anaesth Crit Care Pain Med 2020;39:21–3.

Schnider TW, Minto CF, Shafer SL, et al. The influence of age on propofol pharmacodynamics. Anesthesiology 1999;90:1502–16.

Schnider TW, Minto CF, Gambus PL, et al. The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. Anesthesiology 1998;88:1170–82.

BBUPAsopa. Available: https://bupa.secure.force.com/procedures [Accessed 17 Aug 2015].

BUPA. Available: http://www.cambridgevascularaccess.com/userfiles/BUPAScheduleofProcedures1.pdf

Myles PS, Myles DB, Galagher W, et al. Minimal clinically important difference for three quality of recovery scales. Anesthesiology 2016;125:39–45.

Dundee JW, Robinson FP, McCellum JS, et al. Sensitivity to propofol in the elderly. Anaesthesia 1986;41:482–5.

Bibian S. Automation in clinical anaesthesia, 2006. ISBN: 9780125197750.

Bibian S, Ries CR, Huzmazan M, et al. Introduction to automated drug delivery in clinical anaesthesia. Eur J Control 2005;11:535–57.

Gruber BU, et al. BMJ Open 2022;12:e059919. doi:10.1136/bmjopen-2021-059919