


BMJ Open Comparing propofol anaesthesia guided by Bispectral Index monitoring and frontal EEG wave analysis with standard monitoring in laparoscopic surgery: protocol for the 'EEG in General Anaesthesia - More Than Only a Bispectral Index' Trial, a multicentre, double-blind, randomised controlled trial

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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 postanesthesia 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.^{1,2} 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.³ This index can be used to titrate anaesthetics to the desired depth of anaesthesia.⁴⁻⁹ 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 postanesthesia care unit (PACU) if intravenous anaesthetics are administered.⁹⁻¹⁷ 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.¹⁸⁻²³ 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 neuropharmacology 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.^{24,25} 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.^{26,27} The effectiveness of this teaching method has been confirmed by Bottros *et al*.²⁴ Recently, a different learning curriculum on EEG spectrogram interpretation has been shown to increase residents' knowledge about EEG.²⁸

Rationale and evidence gap

As interindividual variability in the effect-site concentrations of the intravenous anaesthetic propofol to induce and maintain anaesthesia is high,²⁹⁻³¹ 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.³²⁻³⁴ 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.³⁵⁻³⁸ 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*.³⁹⁻⁴²

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),²⁶ 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 'override' 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.^{43 44} 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 remifentanyl to a target effect site concentration of 5 ng/mL. The anaesthesia practitioners will administer anaesthesia uninterrupted from induction to emergence. Paracetamol 1g, ketorolac 30mg, clonidine 150 µg and lidocaine up to 1.5mg/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 4mg 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 Anesthesiology (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

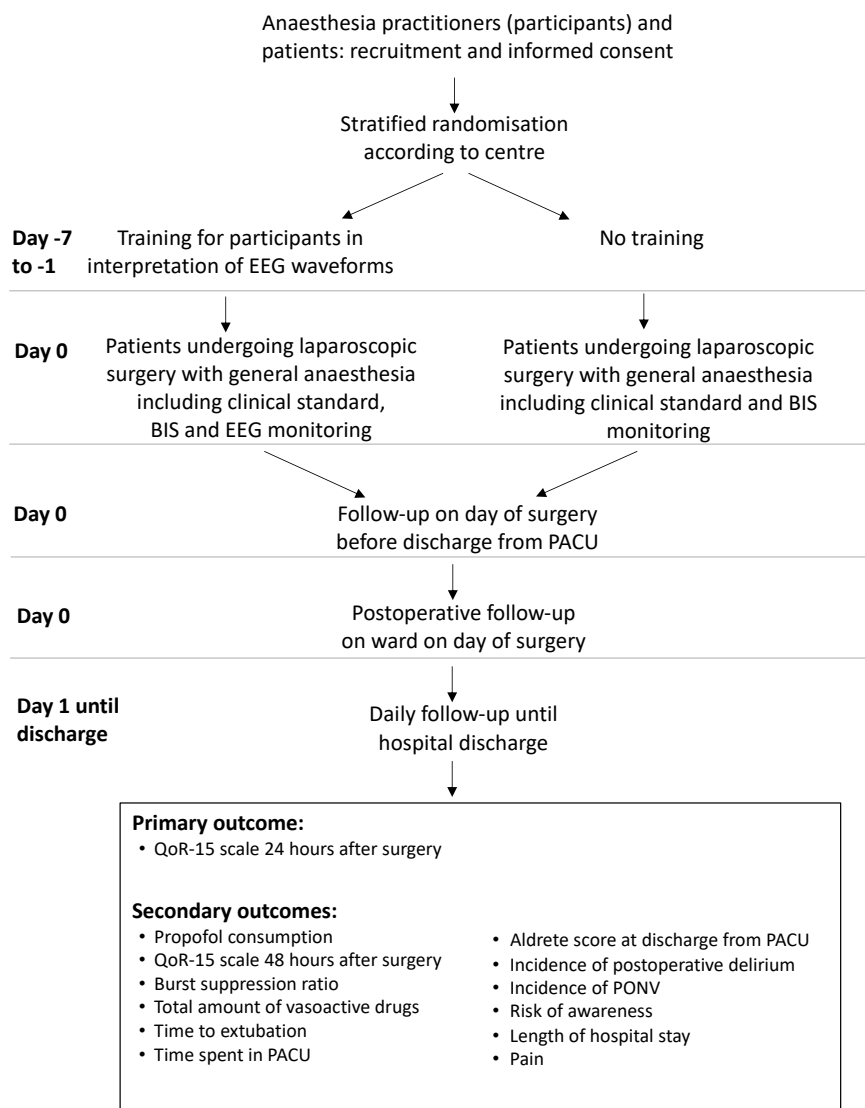


Figure 1 Trial flow chart. BIS, Bispectral Index; EEG, electroencephalogram; PACU, postanesthesia care unit; PONV, postoperative nausea and vomiting; QoR, quality of recovery.

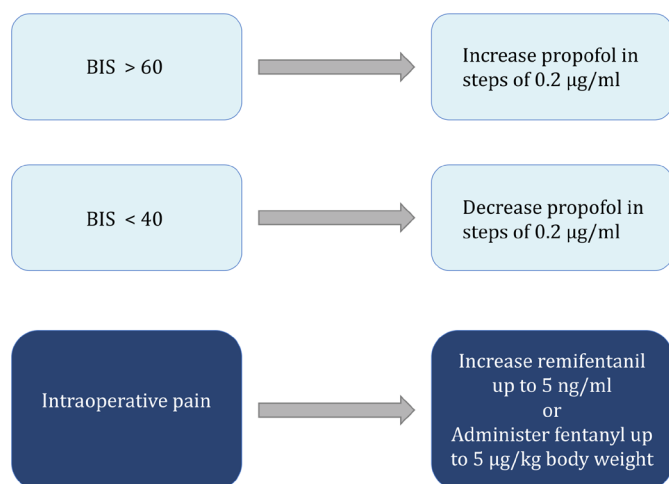


Figure 2 Intraoperative dosing scheme for propofol and opioids. BIS, Bispectral Index.

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).^{45 46} Eligible surgical procedures include laparoscopic hernia repairs (intra-peritoneal 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.¹⁰

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.⁴⁸ 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 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

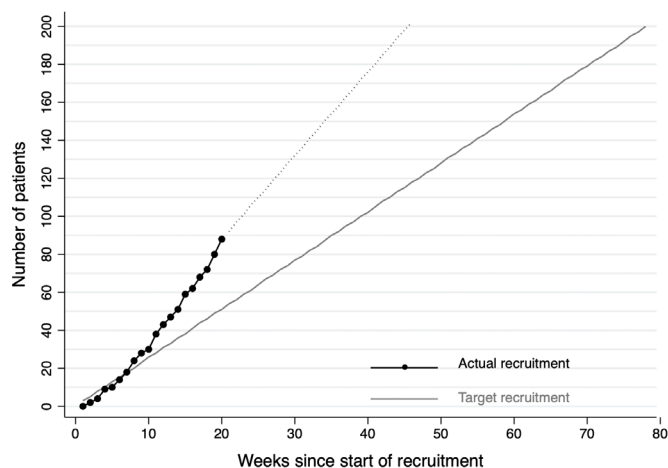


Figure 3 Target and actual recruitment rate of participants (and allocated patients) to achieve the given sample size within the planned recruitment period.

4. Pain measured on a Visual Analogue Scale from 0 to 10
5. Discharge readiness according to the Aldrete Score⁵⁶ at discharge from PACU
6. Risk of awareness according to the Brice interview⁵⁷
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.⁵⁸ 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.⁵⁴ 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).

Ethics and dissemination

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.

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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. LK 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. AL 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. LJ 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. JM 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. LAS has made a substantial contribution to the concept and design of the study protocol, he is the sponsor-investigator of the study. He critically revised the article for important intellectual content and approved 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.

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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.

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