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Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS study protocol

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5 **Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS study**
6 **protocol**
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11 Nina Pirlich¹, Franz Grehn³, Katja Mohnke¹, Konrad Maucher¹, Alexander K. Schuster³, Eva
12 Wittenmeier¹, Irene Schmidtman², Esther M. Hoffmann³

13
14 ¹Department of Anaesthesiology, University Medical Centre of the Johannes Gutenberg-University Mainz, Mainz, Germany

15 ² Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre of the Johannes Gutenberg-University Mainz,
16 Mainz, Germany

17 ³Department of Ophthalmology, University Medical Centre of the Johannes Gutenberg-University Mainz, Mainz, Germany
18
19

20 Correspondence to:

21 Esther M. Hoffmann

22 Augenklinik und Poliklinik

23 Universitätsmedizin Mainz

24 Langenbeckstr. 1

25 55131 Mainz

26 Fax: +496131176620

27 Phone: +496131177085
28
29

30 ehoffman@uni-mainz.de
31
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ABSTRACT

Introduction Neonates and young infants with diagnosed or highly suspected glaucoma require an examination under anaesthesia to achieve accurate intraocular pressure (IOP) measurements, since crying or squinting of the eyes may increase IOP and lead to falsely high values. IOP considerably depends on perioperative variables such as haemodynamic factors, anaesthetics, depth of anaesthesia and airway management. The aim of this paper is to report the design and baseline characteristics of EyeBIS, which is a study to develop a standardized anaesthetic protocol for the measurement of IOP under anaesthesia in childhood glaucoma by investigating the link between the magnitude of IOP and depth of anaesthesia.

Methods and analysis This is a single centre, prospective cohort study in 100 children with diagnosed or highly suspected glaucoma all undergoing ophthalmological examination under general anaesthesia. 20 children, who undergo general anaesthesia for other reasons, are included as controls. The primary outcome measure is the establishment of a standardized anaesthetic protocol for IOP measurement in childhood glaucoma by assessing the relationship between IOP and depth of anaesthesia (calculated as an electroencephalography (EEG) variable, the bispectral index (BIS)), with special emphasis on airway management and haemodynamic parameters. The dependence of IOP under anaesthesia on airway management and haemodynamic parameters will be described, using a mixed linear model. Restricting the model to patients with healthy eyes, will allow to determine a 95% reference region, in which 95% of the measurement values of patients with healthy eyes can be expected.

Ethics and dissemination The study has been approved by the local ethics committee of the Medical Association of the Rhineland-Palatine state, Germany (Approval number: 2019-14207). This work will be disseminated by publication of peer-reviewed manuscripts, presentation in abstract form at national and international scientific meetings and data sharing with other investigators.

Trial registration number [ClinicalTrials.gov NCT03972852](https://clinicaltrials.gov/ct2/show/study/NCT03972852)

Key words: glaucoma, children, intraocular pressure, anaesthesia, standard protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- EyeBIS will be the first study investigating the measurement of IOP in neonates and young infants taking into account the complexity of multifactorial disruptive perioperative factors.
- Data on normal distribution of paediatric IOP are still lacking.
- Cohorts consist of 100 children each with suspected glaucoma and 20 controls without glaucoma, guaranteeing sufficient numbers for statistical analysis.
- Our anaesthetic protocol may provide a recommendation for other glaucoma centres in the future.
- While EyeBIS is a prospective cohort study, it is only single-centre observational study.
- A limitation is the presence of different glaucoma entities as confounding variables and a potentially different susceptibility of IOP measures by multifactorial perioperative disruptive factors (e.g., lowering of the blood pressure and effect of anaesthetics).

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INTRODUCTION

Background and rationale

A basic requirement for diagnosis, monitoring and therapy of childhood glaucoma is the accurate measurement of intraocular pressure (IOP). Despite newer less invasive measurement techniques (rebound technology), neonates and young infants still require an examination under anaesthesia (EUA), either under sedation or general anaesthesia.

Squinting and the elevated stress level following the release of catecholamines may lead to falsely high IOP values and subsequently to inadequate therapy. Success rates for correct measurement of IOP in awake children vary between 14% and 60% in the literature.^{1 2} As congenital glaucoma damage in newborns and young children is exclusively intraocular pressure (IOP) related (i.e. Descemet tears, optic nerve head damage) accurate measurement of IOP under EUA is crucial.

To date, there are no prospective studies from which detailed recommendations on standardized general anaesthesia in children with glaucoma may be derived.

Perioperative anaesthetics include all inhalation anaesthetics and most centrally depressing drugs such as propofol, benzodiazepines and opioids. They result in a reduction of IOP in both healthy and glaucomatous eyes.³ The depth of anaesthesia and IOP reduction are correlated. IOP-lowering effects depend on the applied dose and on the time of administration⁴⁻⁷. The effects of propofol on IOP are mainly known in adult patients, where IOP reduction is suspected to be associated with the lowering of the mean arterial pressure.⁸ Available data on the effect of propofol on IOP in healthy children is inconsistent and there are no data in children with glaucoma.⁹ Furthermore, there are no data on the influence of opioids on the IOP of children with glaucoma.

When applying anaesthesia, airway management also has an influence on IOP.³ Laryngoscopy and intubation can increase IOP substantially, especially when it comes to coughing. However, IOP may rise even without an externally detectable reaction such as a sympatheticotonic cardiovascular mechanism, especially with shallow anaesthesia.¹⁰⁻¹² Laryngeal masks are widely used in adult and paediatric respiratory management and considered safe by paediatric anaesthesiologists in a variety of clinical settings.¹³ Compared to endotracheal intubation in children, the use of laryngeal masks is associated with less cardiovascular reactions and a lesser increase in IOP.¹⁴

The EyeBIS study will be the first study to employ a strict standardized protocol for anaesthesia in children with glaucoma. The study will assess the relationship between depth of anaesthesia and IOP in this population. To determine depth of anaesthesia, the bispectral index (BIS) is used. The index has a range of 0-100 and is a calculated electroencephalography (EEG) variable, used to measure the effects of anaesthetics. A BIS score below 60 indicates the degree of hypnosis of EUA. Both Schäfer and Hanna have described the need to investigate the relationship between depth of anaesthesia and IOP.^{6 15} A correlation between IOP and depth of anaesthesia using BIS in children is already available.¹⁶ The purpose of this manuscript is to report on this protocol in the population described below.

METHODS AND ANALYSIS

Study setting and design

The Department of Ophthalmology, University Medical Center Mainz, has developed an expertise in childhood glaucoma diseases. In the years 2016 and 2017, surgery was performed in approximately 80 children. Since the founding of the German Childhood Glaucoma Centre at the University Medical Center Mainz in June 2017, the number of children receiving a glaucoma diagnosis or surgery has increased significantly. The collaboration between paediatric ophthalmologists and paediatric anaesthesiologists has led to an enhanced focus and expertise in this area and identified the necessity to develop a standardized protocol for general anaesthesia while performing IOP measurements. Established and safe anaesthesia regimens have been modified, taking into account various known factors that influence the measurement of IOP.

With the planned study, we would like to evaluate whether reliable and reproducible measurement values can be generated by a standardized protocol. The EyeBIS trial is a prospective, single-centre, non-randomized clinical trial.

Trial population and eligibility criteria

Children in the age group 6 months to 10 years will be included, when meeting the following criteria: requirement of EUA with a laryngeal mask for a surgical or diagnostic procedure; suspected glaucoma or control children undergoing ocular surgery other than glaucoma surgery (control group); ASA classification 1, 2 or 3; and informed written consent from one of their legal representatives.

Patients will not be included in this trial if they meet one or more of the following criteria: contraindications to the use of a laryngeal mask (e.g., severe infections; tumour or bleeding in the upper airway tract, which might prevent the sufficient placement of the laryngeal mask; if the expected magnitude of ventilation pressure exceeds the upper leakage pressure of the laryngeal mask (40 cm H₂O); the necessity of a constant tracheal access; patients with a severe gastro-oesophageal reflux; or interference of the laryngeal mask with the surgical approach), or known allergy to propofol or remifentanyl. Eligibility criteria are shown in Figure 1.

Recruitment and participant timelines

Participant inclusion started in June 2019 in the Childhood Glaucoma Centre at the University Medical Centre, Mainz, Germany. The history and physical examinations of all patients scheduled for surgery were screened preoperatively for predictors of difficult airway, oesophageal reflux and allergies.

Patient will be informed about the study by an investigator. Patients will be included if they require the insertion of a laryngeal mask under general anaesthesia. Informed consent for all paediatric participants will be obtained from one of their legal representatives. This also includes information and consent according to the German Medical Privacy Rules (DSGVO, in analogy to the US Insurance Portability and Accountability Act of 1996 (HIPAA)). Prospective approval of the study will be granted by the local ethics committee of the Medical Association of the Rhineland-Palatine state, Germany (approval number: 2019-14207). The Clinical Trials registration number of the study is ClinicalTrials.gov NCT03972852.

The schedule of study enrolment is shown in Figure 2.

Intervention

Induction and maintenance of EUA is performed. In the present study, the laryngeal mask Ambu® AuraGain™ (German distribution by Ambu GmbH, Bad Nauheim, Germany) is used, which is a

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2
3 second-generation laryngeal mask with integrated gastric access and the possibility of fiberoptic
4 intubation.¹⁷ Compression of the cervical vessels through the cuff of laryngeal masks has been
5 reported in adults.¹⁸ It has not been investigated whether the blockage of a laryngeal mask in
6 children has an influence on IOP by obstructing the venous return. According to the standard
7 operating procedures of the Department of Anaesthesiology, a premedication with oral midazolam
8 (juice) is administered when the patient is collected from the ward. A dosage of 0.5 mg/kg (up to a
9 maximum dose of 10 mg) is given.
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12 Local anaesthetics are applied topically to two possible puncture sites at least 1 h prior to surgery.
13 Before induction of anaesthesia, intravenous (i.v.) access is established. The child's head is positioned
14 in a neutral way in a head ring, with the body in a flat back position. To optimize mask ventilation,
15 the shoulder blades are padded with a rolled-up surgical tissue.
16
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18 The induction and maintenance of EUA is performed by an anaesthesiologist, specifically educated in
19 anaesthesia for neonates and young infants. Before initiating the EUA, pulse oximetry monitoring,
20 ECG, non-invasive blood pressure measurement and the BIS are started.
21

22 Preoxygenation takes place with a FiO_2 of 0.8 and a fresh gas flow of 7 l/min.
23

24 As soon as the BIS measurement starts, the BIS value and an initial blood pressure value is noted.
25

26 If it is possible to establish i.v. access, an initial propofol bolus of 2-4 mg/kg body weight is applied.
27 The children are breathing spontaneously. When the oxygen saturation drops below 90%, a
28 ventilation via a face mask takes place.
29

30 The schedule of interventions is also summarized in Figure 2.
31

32 IOP measurements take place during different depths of anaesthesia. A first IOP measurement is
33 performed when sufficient sedation for IOP measurement after titrated propofol application (2-4
34 mg/kg or more if necessary) is achieved. A second IOP measurement is carried out 60 s after
35 placement of the laryngeal mask to avoid a potentially falsely high IOP value due to a direct
36 sympathetic reaction caused by the laryngeal mask placement. Then, a third IOP measurement is
37 taken after a break of 60 s directly after blockage of the cuff of the laryngeal mask (60 cmH₂O).
38
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40 IOP measurement of each eye is performed with the iCare® PRO tonometer followed by a
41 measurement with the Perkins applanation tonometer after a one-minute waiting time to avoid
42 potential influence of repetitive measurements on IOP.
43

44 Central corneal thickness (CCT) has an influence on IOP measurement in adults and children and is
45 measured in this study.¹⁹ CCT has also been shown to be a relevant factor in the evaluation of
46 childhood glaucoma in many studies and appears to result in significant differences in the
47 measurement of IOP, depending on the device used.²⁰ This is why two different devices are used in
48 this study. All IOP measurements are performed by one of four expert study investigators.
49
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51 The Perkins Mk3 is available for measuring IOP. The Perkins Mk3 is a mobile, battery-powered
52 applanation tonometer, which consists of the following components: a forehead support for correct
53 placement, a handgrip for the examiner, a LED light source with a blue filter, a biprism and a force
54 transducer. The force transducer measures how much force the examiner must use to flatten the
55 cornea to a defined circular area of 4.8 mm² (diameter 3.06 mm). For the visualization of the edge of
56 this surface, fluoresceine (a fluorescent dye) is applied in advance to the cornea. In compliant adults
57 the awake patient is examined after topical application of a local anaesthetic.
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3 The system draws on the 1965 prototype developed by Perkins.²¹ It has been specifically designed to
4 measure IOP in patients who cannot adequately sit upright at a standard stationary applanation
5 tonometer.
6

7 The iCare® ProTonometer (iCare Finland Oy, 01510 Vantaa, Finland, German distribution by bon
8 Optic Vertriebsgesellschaft GmbH, Lübeck, Germany) has been available for in-and outpatient as well
9 as self-tonometry since its certification in 2010. The iCare® PRO Tonometer is a mobile, battery-
10 operated rebound or induction tonometer, which consists of the following components: a forehead
11 support for correct placement, a handle for the examiner and a miniaturized measuring head. The
12 measuring head bounces against the cornea from a short distance in six, very short individual
13 measurements. Depending on the IOP, the measuring head is slowed down to varying degrees, from
14 which the device calculates the IOP using magnetic coils. The compliant awake patient does not
15 require local anaesthesia. Only a few studies have compared the two techniques in children.^{22 23}
16
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19 **Central corneal thickness measurement**

20 Measurement of central corneal thickness is performed by Tomey AL-3000 (Tomey GmbH, Nurnberg,
21 Germany). The SP-3000 is an ophthalmic diagnosis instrument which acquires corneal thickness, by
22 using ultrasonic waves that are transmitted from the ultrasonic oscillator enclosed in the probe. One
23 measurement is performed in each eye.
24
25

26 In addition to IOP measurements, BIS values, blood pressure (including mean arterial pressure), heart
27 rate and oxygen saturation are documented for each time point of IOP measurement. General
28 anaesthesia is maintained with a syringe pump of propofol at a rate of 4-5 mg/kg/h and a syringe
29 pump of remifentanyl with a running rate of 0.3 µg/kg/min. In case an i.v. access is initially not
30 possible, mask induction of EUA via sevoflurane (4 vol%, flow 7 l/min, FiO₂ 0.8) is performed,
31 followed by the establishment of an i.v. access.
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34 Figure 3 presents all interventions on a time scale.
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38 **Bispectral Index Monitoring**

39 The study uses the Aspect XP Bispectral Index Monitor (Medtronic Inc, Minneapolis, MN 55432,
40 USA). It is available for intraclinical brain function monitoring by deriving raw EEG signals from
41 patients for perioperative or intensive care monitoring, as well as for clinical research.
42
43

44 As described in the introduction, the BIS, with a dimension of 0-100, is a calculated EEG variable and
45 can be used to aid in assessing the effects of anaesthetics. A BIS score below 60 indicates the degree
46 of hypnosis of general anaesthesia. The measurement is carried out by a sensor fitted for the
47 paediatric anatomy (BISTM Paediatric Sensor), which is mounted on the forehead of the patient.
48
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50 Data from children who had to undergo mask induction are excluded from the main analysis and
51 analyzed separately. Criteria to cancel the intervention include an unexpectedly difficult airway, an
52 unrecoverable laryngeal mask leak, a different need for endotracheal intubation, and circulatory
53 instability requiring intervention.
54

55 **Outcomes measures**

56 Aim of this paper is to report design and baseline characteristics of EyeBIS, a study to develop a
57 standardised anaesthetic protocol for the measurement of IOP under general anaesthesia in
58 childhood glaucoma by investigating the partial correlation between the magnitude of IOP and depth
59 of anaesthesia adjusting for potential confounders.
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3 Secondary outcome measures in future studies include the comparison of two different IOP
4 measurements methods (applanation tonometry and rebound tonometry), the magnitude of the
5 paediatric IOP during EUA in relation to cuff pressure of the laryngeal mask, regarding end
6 expiratory CO₂ pressure, blood pressure and heart frequency and the definition of the normal range
7 of the paediatric IOP, as well as the correlation of the CCT and IOP (determined by regression of IOP
8 on CCT).
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11 Primary and secondary outcomes are also shown in Figure 1.
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14 15 **Data collection, management and analysis**

16 Data collection and management of the present study

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19 For data collection, a paper-based case report form (CRF) was developed and is used for each
20 patient. In addition to all other documentation, the CRF and the patient's study file belongs to the
21 source data. The CRF contains information that is requested directly from the patient and thus
22 cannot be verified on the basis of the patient's study file (screening information and data collected in
23 the OR).
24
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26 For pseudonymization purposes, every patient is coded with a specific patient number. In addition to
27 the paper-based form, this study is also documented electronically. For this purpose, all information
28 from the study file and the CRF are transferred to the computer in a tabular form.
29
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31 Access to data

32 Data management of the present study is performed by the main investigator. All electronically
33 stored data are backed up regularly. The pseudonymity of patients is ensured throughout the
34 evaluation. All study data, including the electronically recorded data, will be archived and kept for at
35 least 15 years after completion of the study according to the currently valid ICH Guidelines on Good
36 Clinical Practice (GCP) E6 (R2). Data are accessible to all participating personnel and monitors. The
37 database management system is capable of producing accurate and complete copies of the data in
38 visual form for inspection by government agencies or ethics committees. Enrolled patients and their
39 authorised representative have been informed about this.
40
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42 Monitoring

43 Prior to enrolling patients, the investigators were briefed on the CRF and study protocol. All
44 documents required for data collection are available in the operating theatre. Each CRF is filled in by
45 the investigator after the measurements have been performed. The data is then promptly entered
46 electronically under his supervision. The investigator regularly evaluates the progress of data
47 collection and study outcomes in order to address any emerging data collection issues at an early
48 stage. The data monitoring is managed and analysed in accordance with the ICH GCP Guideline E6
49 (R2) and followed the requirements of German Drug Law.
50
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52 Adverse events will be recorded after patient enrolment. The study will be temporarily interrupted
53 by the attending investigator at any time on the individual subject, if a serious adverse event is
54 suspected, which may be associated with IOP measurement or an airway device being used. A
55 suspected adverse event or adverse reaction will be considered serious when it comes to one of the
56 following events: death, a life threatening reaction leading to inpatient hospitalization, and a persistent
57 or significant incapacity or substantial disability of the normal age-adapted life functions. If the
58 protocol is discontinued as a result of an adverse event, study personnel will document the
59 circumstances and data leading to the discontinuation of measurement. The principal investigator
60

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3 will inform the local research ethics committee (REC) in case of a severe adverse event following
4 local standard operating procedures.
5

6 The Clinical Research Unit of the Department of Anaesthesiology, University Center Mainz inspects
7 and reviews screening forms and clinical data at regular intervals.
8

9 **Sample size considerations**

10 With the envisaged number of 100 subjects, a single IOP measurement of one eye and parallel
11 determination of the BIS, the null hypothesis "correlation = 0" can be rejected at the 5% level with
12 86.5% if the correlation amounts to 0.3. If the actual correlation is 0.35, the power rises to 95%. The
13 multiple measurements provide additional information, resulting in a power gain. It is not yet
14 possible to anticipate how strong the correlation between the multiple measurements will be. With
15 decreasing correlation between repeat measurements power increases and, similarly, the smaller
16 correlation between IOP and BIS are still detectable with sufficient power.
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19 **Statistical analysis**

20 For statistical analysis, SAS statistical software will be used. The analysis corresponds to the
21 CONSORT statement for non-pharmacological interventions.
22
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24 **Description of patient group at baseline**

25 The baseline features of patients will be described using absolute numbers (n) and percentages for
26 categorical variables and the minimum, maximum, mean and standard deviation for normally
27 distributed variable and as median (IQR) for non-Gaussian variables. The Pearson correlation
28 coefficient will be used to compare patient specifics between the groups and the baseline.
29
30

31 **Analysis of the primary outcome**

32 The relationship between the IOP and BIS will be investigated using a mixed linear model. In this, IOP
33 is the dependent variable, the BIS is the independent variable. Random effects are subject and eye
34 (of a subject).
35
36

37 **Analysis of the secondary outcome**

38 To compare the two measurement methods for IOP, applanation tonometry and rebound
39 tonometry, Bland-Altman diagrams will be created.
40

41 The dependence of IOP under general anaesthesia on the cuff pressure of the laryngeal mask, the
42 end tidal CO₂ partial pressure, the blood pressure and the heart rate will also be described by a
43 mixed linear model, with the variables of interest as covariates and random effects for subject and
44 eye and adjustment for corneal thickness.
45

46 For children without glaucoma, a quantile regression will be performed that takes into account the
47 factors mentioned above. From this, it is possible to deduce standard ranges in which e.g. 90% or
48 95% of the values of healthy children are expected.
49

50 **Subgroup analysis**

51 Data from children who had to undergo mask induction will be analysed separately.
52

53 **DISCUSSION**

54 Several studies have documented various variables that have an impact on the paediatric IOP [3]. The
55 weakness of the previously published studies is that none has examined all in a single study setting.
56 To our current knowledge, the EyeBIS study is the only clinical study of its kind to associate IOP in
57 100 childhood glaucoma patients and 20 non-glaucoma patients (control group) with the depth of
58 anaesthesia under the best possible standardized environmental conditions. Due to the exclusivity
59 and safety of our patient population.
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3 In conclusion, if our study will find a partial correlation between BIS and IOP this could lead to more
4 reliable IOP data in childhood glaucoma examinations under anaesthesia. This protocol could be a
5 reference standard for children with suspected glaucoma who cannot undergo an examination while
6 awake. This leads to an improved, more reliable ability to diagnose glaucoma with an earlier therapy,
7 which overall leads to a significantly better functional outcome for children.
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10 11 **ETHICS AND DISSEMINATION**

12 **Research ethics approval**

13 The requirements of the ICH Guideline for Good Clinical Practice (GCP) E6 of June 1996 and of
14 CPMP/ICH/135/95 of September 1997 are, in addition to the national laws and the Declaration of
15 Helsinki (Somerset West 1996), the basis for carrying out this study.
16

17 All study personnel are obliged to participate in this study according to these guidelines.
18

19 **Consent or assent**

20 Before being included in the study, the study will be verbally and comprehensibly explained to
21 patient and one of his/her authorized representatives by a clinical study investigator, as required by
22 German law. He/she will also receive a comprehensively written information sheet. The authorized
23 representatives will have the opportunity to have an informed discussion with the clinical study
24 investigator about the study.
25

26 The clinical study investigator will obtain written consent from the authorized representatives willing
27 to participate in the trial. The information leaflet and a new execution of the consent document will
28 be handed over to one of the authorized representatives. Upon request, the patient will receive a
29 child-friendly version of the information leaflet.
30

31 The authorised representative may withdraw from the study at any time if he/she is unwilling to
32 continue in the trial. In this case, the data from a patient who requests full withdrawal will not be
33 considered in the data analysis.
34

35 **Confidentiality**

36 All original documents will be kept in the clinical research unit for the next 15 years. The study data
37 will be handled as requested by the German Federal Data Protection Act, which implements the
38 Directive 95/46/EC on data protection (Data Protection Directive). All original records will be kept on
39 file at the trial sites or coordinating data managing centre for 15 years. The cleaned electronic trial
40 database file will be anonymized and kept on file for 15 years.
41

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44 Anaesthesiology and Ophthalmology for their great effort and support for this study. They also thank
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46

47 **Author contributions**

48 The study concept and design were conceived by NP, EMH, KoM, IS and EW. NP, EMH and KoM are
49 conducting screening and data collection. Analysis and interpretation of data will be performed by IS,
50 NP, EMH, KoM, FG and AKS. KM and NP prepared the first draft of the manuscript. All authors have
51 provided edits and critiqued the manuscript for intellectual content, as well as have given final
52 approval for manuscript submission. Results of this study will be part of the doctoral thesis of KoM.
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Provenance and peer review

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The results of this study will be presented at conferences and published in peer reviewed journals

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2
3 **Figure captions**
4

5 Figure 1:
6

7 Study flow chart according to American Society of Anaesthesiologists (ASA) with inclusion
8 and exclusion criteria, as well as outcome measures
9

10 Figure 2:
11

12 Schedule of study enrolment and interventions. i.v., intravenous; SpO₂, oxygen saturation;
13 ECG, electrocardiography; BIS, bispectral index; IOP, intraocular pressure.
14

15 Figure 3:
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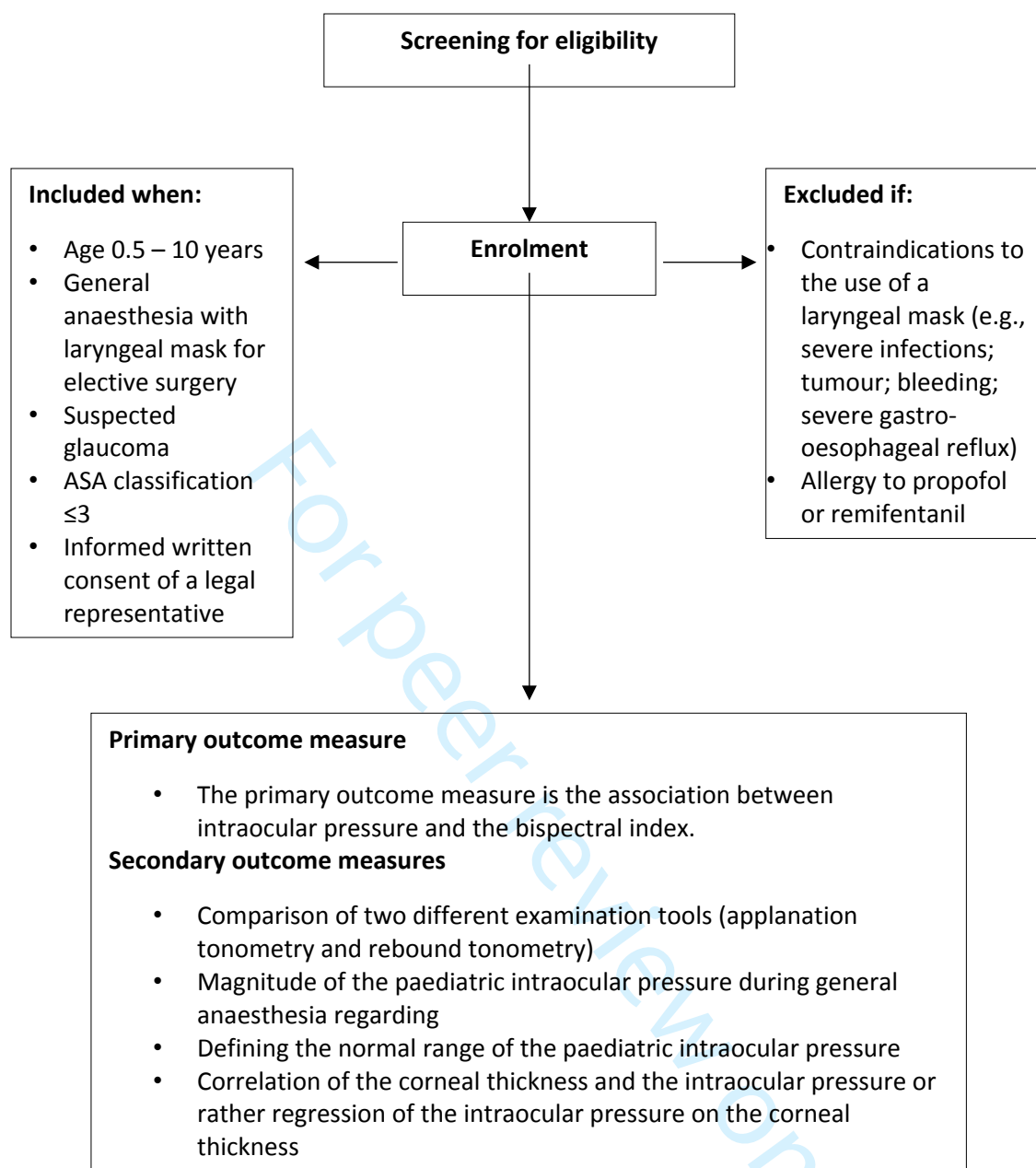
17 EyeBIS worksheet. Detailed layout of all steps on the interventional time scale
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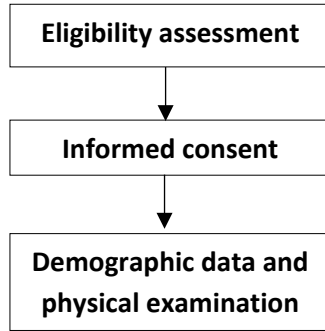
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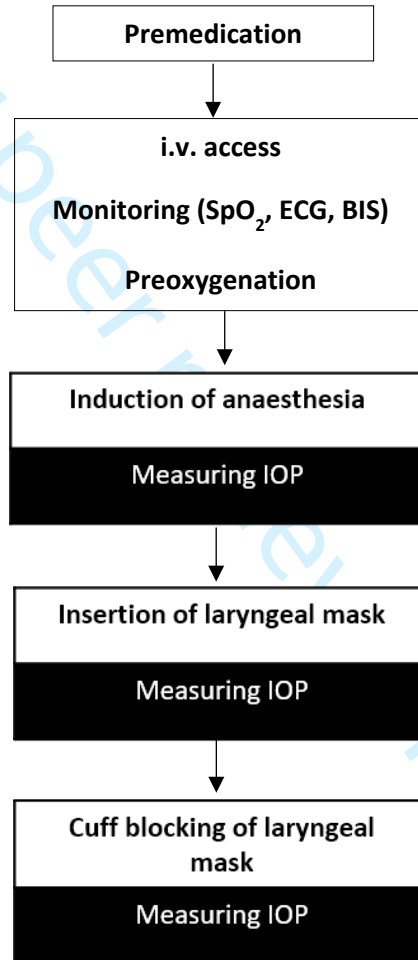
For peer review only



Day 0



Day 1



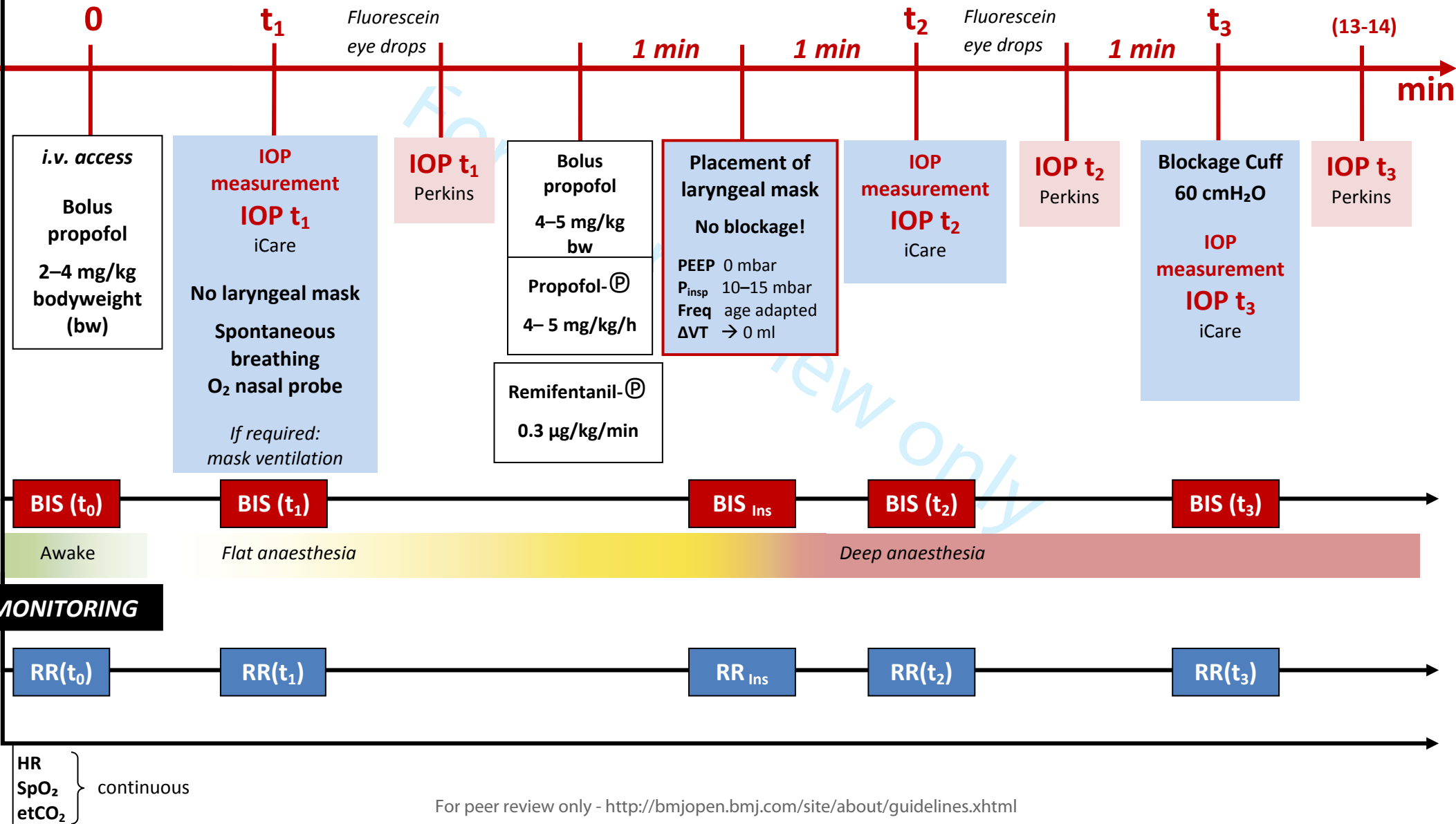


eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

$FiO_2 = 0.8$
Fresh gas flow 7 l/min



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

1	Roles and	#5b	Name and contact information for the trial sponsor	11
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	11
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate authority	
12			over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	11
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for undertaking	4
28	rationale		the trial, including summary of relevant studies (published and	
29			unpublished) examining benefits and harms for each intervention	
30				
31				
32	Background and	#6b	Explanation for choice of comparators	4
33	rationale: choice of			
34	comparators			
35				
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37	Objectives	#7	Specific objectives or hypotheses	4
38				
39				
40	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
41			group, crossover, factorial, single group), allocation ratio, and	
42			framework (eg, superiority, equivalence, non-inferiority,	
43			exploratory)	
44				
45				
46	Methods:			
47	Participants,			
48	interventions, and			
49	outcomes			
50				
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53	Study setting	#9	Description of study settings (eg, community clinic, academic	5
54			hospital) and list of countries where data will be collected.	
55			Reference to where list of study sites can be obtained	
56				
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
2				
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
7	description			
8				
9				
10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
11	modifications			
12				
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14				
15	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
16	adherence			
17				
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21	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
22	concomitant care			
23				
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25	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
26				
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34	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
35				
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40	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
41				
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45	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
46				
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48				
49	Methods: Assignment			
50	of interventions (for			
51	controlled trials)			
52				
53				
54	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	n/a
55	generation			
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provided in a separate document that is unavailable to those who enrol participants or assign interventions

Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	8
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	9

1	Statistics: additional	#20b	Methods for any additional analyses (eg, subgroup and adjusted	9
2	analyses		analyses)	
3				
4	Statistics: analysis	#20c	Definition of analysis population relating to protocol non-	9
5	population and missing		adherence (eg, as randomised analysis), and any statistical	
6	data		methods to handle missing data (eg, multiple imputation)	
7				
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10	Methods: Monitoring			
11				
12	Data monitoring:	#21a	Composition of data monitoring committee (DMC); summary of	8
13	formal committee		its role and reporting structure; statement of whether it is	
14			independent from the sponsor and competing interests; and	
15			reference to where further details about its charter can be found,	
16			if not in the protocol. Alternatively, an explanation of why a	
17			DMC is not needed	
18				
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22	Data monitoring:	#21b	Description of any interim analyses and stopping guidelines,	n/a
23	interim analysis		including who will have access to these interim results and make	
24			the final decision to terminate the trial	
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26				
27	Harms	#22	Plans for collecting, assessing, reporting, and managing solicited	9
28			and spontaneously reported adverse events and other unintended	
29			effects of trial interventions or trial conduct	
30				
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33	Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and	9
34			whether the process will be independent from investigators and	
35			the sponsor	
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38	Ethics and			
39	dissemination			
40				
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42	Research ethics	#24	Plans for seeking research ethics committee / institutional review	5
43	approval		board (REC / IRB) approval	
44				
45				
46	Protocol amendments	#25	Plans for communicating important protocol modifications (eg,	n/a
47			changes to eligibility criteria, outcomes, analyses) to relevant	
48			parties (eg, investigators, REC / IRBs, trial participants, trial	
49			registries, journals, regulators)	
50				
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53	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial	10
54			participants or authorised surrogates, and how (see Item 32)	
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1	Consent or assent:	#26b	Additional consent provisions for collection and use of	10
2	ancillary studies		participant data and biological specimens in ancillary studies, if	
3			applicable	
4				
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6	Confidentiality	#27	How personal information about potential and enrolled	11
7			participants will be collected, shared, and maintained in order to	
8			protect confidentiality before, during, and after the trial	
9				
10				
11	Declaration of interests	#28	Financial and other competing interests for principal investigators	11
12			for the overall trial and each study site	
13				
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15	Data access	#29	Statement of who will have access to the final trial dataset, and	8
16			disclosure of contractual agreements that limit such access for	
17			investigators	
18				
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20	Ancillary and post trial	#30	Provisions, if any, for ancillary and post-trial care, and for	n/a
21	care		compensation to those who suffer harm from trial participation	
22				
23				
24	Dissemination policy:	#31a	Plans for investigators and sponsor to communicate trial results	n/a
25	trial results		to participants, healthcare professionals, the public, and other	
26			relevant groups (eg, via publication, reporting in results	
27			databases, or other data sharing arrangements), including any	
28			publication restrictions	
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33	Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	11
34	authorship		professional writers	
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37	Dissemination policy:	#31c	Plans, if any, for granting public access to the full protocol,	n/a
38	reproducible research		participant-level dataset, and statistical code	
39				
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41	Appendices			
42				
43	Informed consent	#32	Model consent form and other related documentation given to	n/a
44	materials		participants and authorised surrogates	
45				
46				
47	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	n/a
48			biological specimens for genetic or molecular analysis in the	
49			current trial and for future use in ancillary studies, if applicable	
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BMJ Open

Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS study protocol

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Manuscript ID	bmjopen-2020-045906.R1
Article Type:	Protocol
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Primary Subject Heading:	Ophthalmology
Secondary Subject Heading:	Anaesthesia, Ophthalmology, Paediatrics, Patient-centred medicine, Research methods
Keywords:	Anaesthesia in ophthalmology < ANAESTHETICS, Paediatric anaesthesia < ANAESTHETICS, Glaucoma < OPHTHALMOLOGY, Paediatric ophthalmology < OPHTHALMOLOGY

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5 **Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS**
6 **study protocol**
7

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9 Nina Pirlich¹, Franz Grehn³, Katja Mohnke¹, Konrad Maucher¹, Alexander K.
10 Schuster³, Eva Wittenmeier¹, Irene Schmidtman², Esther M. Hoffmann³
11

12 ¹Department of Anaesthesiology, University Medical Centre of the Johannes Gutenberg-
13 University Mainz, Mainz, Germany

14 ² Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre
15 of the Johannes Gutenberg-University Mainz, Mainz, Germany

16 ³Department of Ophthalmology, University Medical Centre of the Johannes Gutenberg-
17 University Mainz, Mainz, Germany
18
19
20
21

22 Correspondence to:
23 Esther M. Hoffmann
24 Augenklinik und Poliklinik
25 Universitätsmedizin Mainz
26 Langenbeckstr. 1
27 55131 Mainz
28 Fax: +496131176620
29 Phone: +496131177085
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32 ehoffman@uni-mainz.de
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ABSTRACT

Introduction Neonates and young infants with diagnosed or highly suspected glaucoma require an examination under anaesthesia to achieve accurate intraocular pressure (IOP) measurements, since crying or squinting of the eyes may increase IOP and lead to falsely high values. IOP considerably depends on perioperative variables such as haemodynamic factors, anaesthetics, depth of anaesthesia and airway management. The aim of this paper is to report the design and baseline characteristics of EyeBIS, which is a study to develop a standardized anaesthetic protocol for the measurement of IOP under anaesthesia in childhood glaucoma by investigating the link between the magnitude of IOP and depth of anaesthesia.

Methods and analysis This is a single centre, prospective cohort study in 100 children with diagnosed or highly suspected glaucoma all undergoing ophthalmological examination under general anaesthesia. 20 children, who undergo general anaesthesia for other reasons, are included as controls. The primary outcome measure is the establishment of a standardized anaesthetic protocol for IOP measurement in childhood glaucoma by assessing the relationship between IOP and depth of anaesthesia (calculated as an electroencephalography (EEG) variable, the bispectral index (BIS)), with special emphasis on airway management and haemodynamic parameters. The dependence of IOP under anaesthesia on airway management and haemodynamic parameters will be described, using a mixed linear model. Restricting the model to patients with healthy eyes, will allow to determine a 95% reference region, in which 95% of the measurement values of patients with healthy eyes can be expected.

Ethics and dissemination The study has been approved by the local ethics committee of the Medical Association of Rhineland-Palatine (Ethik-Kommission der Landesärztekammer Rheinland-Pfalz), Germany (Approval number: 2019-14207). This work will be disseminated by publication of peer-reviewed manuscripts, presentation in abstract form at national and international scientific meetings and data sharing with other investigators.

Trial registration number ClinicalTrials.gov NCT03972852

Key words: glaucoma, children, intraocular pressure, anaesthesia, standard protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- EyeBIS will be the first study investigating the measurement of IOP in neonates and young infants taking into account the complexity of multifactorial disruptive perioperative factors.
- EyeBIS will provide data on distribution of paediatric intraocular pressure.
- The developed protocol may provide a recommendation for other glaucoma centres.
- It is only a single-centre observational study.

For peer review only

INTRODUCTION

Background and rationale

A basic requirement for diagnosis, monitoring and therapy of childhood glaucoma is the accurate measurement of intraocular pressure (IOP). Despite newer less invasive measurement techniques (rebound technology), neonates and young infants still require an examination under anaesthesia (EUA), either under sedation or general anaesthesia.

Squinting and the elevated stress level following the release of catecholamines may lead to falsely high IOP values and subsequently to inadequate therapy. Success rates for correct measurement of IOP in awake children vary between 14% and 60% in the literature.^{1 2} As congenital glaucoma damage in newborns and young children is exclusively intraocular pressure (IOP) related (i.e. Descemet tears, optic nerve head damage) accurate measurement of IOP under EUA is crucial.

To date, there are no prospective studies from which detailed recommendations on standardized general anaesthesia in children with glaucoma may be derived.

Perioperative anaesthetics include all inhalation anaesthetics and most centrally depressing drugs such as propofol, benzodiazepines and opioids. They result in a reduction of IOP in both healthy and glaucomatous eyes.³ The depth of anaesthesia and IOP reduction are correlated. IOP-lowering effects depend on the applied dose and on the time of administration⁴⁻⁷. The effects of propofol on IOP are mainly known in adult patients, where IOP reduction is suspected to be associated with the lowering of the mean arterial pressure.⁸ Available data on the effect of propofol on IOP in healthy children is inconsistent and there are no data in children with glaucoma.⁹ Furthermore, there are no data on the influence of opioids on the IOP of children with glaucoma.

When applying anaesthesia, airway management also has an influence on IOP.³ Laryngoscopy and intubation can increase IOP substantially, especially when it comes to coughing. However, IOP may rise even without an externally detectable reaction such as a sympathicotonic cardiovascular mechanism, especially with shallow anaesthesia.¹⁰⁻¹² Laryngeal masks are widely used in adult and paediatric respiratory management and considered safe by paediatric anaesthesiologists in a variety of clinical settings.¹³ Compared to endotracheal intubation in children, the use of laryngeal masks is associated with less cardiovascular reactions and a lesser increase in IOP.¹⁴

The EyeBIS study will be the first study to employ a strict standardized protocol for anaesthesia in children with glaucoma. The study will assess the relationship between depth of anaesthesia and IOP in this population. To determine depth of anaesthesia, the bispectral index (BIS) is used. The index has a range of 0-100 and is a calculated electroencephalography (EEG) variable, used to measure the effects of anaesthetics. A BIS score below 60 indicates the degree of hypnosis of EUA. Both Schäfer and Hanna have described the need to investigate the relationship between depth of anaesthesia and IOP.^{6 15} A correlation between IOP and depth of anaesthesia using BIS in children is already available.¹⁶ The purpose of this manuscript is to report on this protocol in the population described below.

METHODS AND ANALYSIS

Study setting and design

The Department of Ophthalmology, University Medical Center Mainz, has developed an expertise in childhood glaucoma diseases. In the years 2016 and 2017, surgery was performed in approximately 80 children. Since the founding of the German Childhood Glaucoma Centre at the University Medical Center Mainz in June 2017, the number of children receiving a glaucoma diagnosis or surgery has increased significantly. The collaboration between paediatric ophthalmologists and paediatric anaesthesiologists has led to an enhanced focus and expertise in this area and identified the necessity to develop a standardized protocol for general anaesthesia while performing IOP measurements. Established and safe anaesthesia regimens have been modified, taking into account various known factors that influence the measurement of IOP.

With the planned study, we would like to evaluate whether reliable and reproducible measurement values can be generated by a standardized protocol. The EyeBIS trial is a prospective, single-centre, non-randomized clinical trial.

Patient and Public Involvement

Patients of this research were first involved in June 2019 by the research team (NP and EMH, and medical students). Eligible patients (see section below) were asked whether they are interested in this study. Inclusion criteria were discussed with parents and children and patients were examined according to the individual standards and SOPs of the Clinic for Anaesthesiology and the Dept. of Ophthalmology. Patients were not involved in the development and design of the study protocol. The public was not involved. Study results will not be disseminated to participants specifically. However, if participants are interested in the results of the research they will receive any information, the manuscript, and published research on this topic in the future.

Trial population and eligibility criteria

Children in the age group 6 months to 10 years will be included, when meeting the following criteria: requirement of EUA with a laryngeal mask for a surgical or diagnostic procedure; suspected glaucoma or control children undergoing ocular surgery other than glaucoma surgery (control group); ASA classification 1, 2 or 3; and informed written consent from one of their legal representatives.

Patients will not be included in this trial if they meet one or more of the following criteria: contraindications to the use of a laryngeal mask (e.g., severe infections; tumour or bleeding in the upper airway tract, which might prevent the sufficient placement of the laryngeal mask; if the expected magnitude of ventilation pressure exceeds the upper leakage pressure of the laryngeal mask (40 cm H₂O); the necessity of a constant tracheal access; patients with a severe gastro-oesophageal reflux; or interference of the laryngeal mask with the surgical approach), or known allergy to propofol or remifentanyl. Eligibility criteria are shown in Figure 1.

Recruitment and participant timelines

Participant inclusion started in June 2019 in the Childhood Glaucoma Centre at the University Medical Centre, Mainz, Germany. The history and physical examinations of all patients scheduled for surgery were screened preoperatively for predictors of difficult airway, oesophageal reflux and allergies.

Patient will be informed about the study by the investigators and medical students (EMH, NP) Patients will be included if they require the insertion of a laryngeal mask under general

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2
3 anaesthesia. Informed consent for all paediatric participants will be obtained from one of their
4 legal representatives. This also includes information and consent according to the German
5 Medical Privacy Rules (DSGVO, in analogy to the US Insurance Portability and
6 Accountability Act of 1996 (HIPAA)). Prospective approval of the study will be granted by the
7 local ethics committee of the Medical Association of the Rhineland-Palatine state (Ethik-
8 Kommission der Landesärztekammer Rheinland-Pfalz), Germany (approval number: 2019-
9 14207). The Clinical Trials registration number of the study is ClinicalTrials.gov
10 NCT03972852.
11

12
13 The schedule of study enrolment is shown in Figure 2.
14

15 16 **Intervention**

17 Induction and maintenance of EUA is performed. In the present study, the laryngeal mask
18 Ambu® AuraGain™ (German distribution by Ambu GmbH, Bad Nauheim, Germany) is used,
19 which is a second-generation laryngeal mask with integrated gastric access and the
20 possibility of fiberoptic intubation.¹⁷ Compression of the cervical vessels through the cuff of
21 laryngeal masks has been reported in adults.¹⁸ It has not been investigated whether the
22 blockage of a laryngeal mask in children has an influence on IOP by obstructing the venous
23 return. According to the standard operating procedures of the Department of
24 Anaesthesiology, a premedication with oral midazolam (juice) is administered when the
25 patient is collected from the ward. A dosage of 0.5 mg/kg (up to a maximum dose of 10 mg)
26 is given.
27

28
29 Local anaesthetics are applied topically to two possible puncture sites at least 1 h prior to
30 surgery. Before induction of anaesthesia, intravenous (i.v.) access is established. The child's
31 head is positioned in a neutral way in a head ring, with the body in a flat back position. To
32 optimize mask ventilation, the shoulder blades are padded with a rolled-up surgical tissue.
33

34
35 The induction and maintenance of EUA is performed by an anaesthesiologist, specifically
36 educated in anaesthesia for neonates and young infants. Before initiating the EUA, pulse
37 oximetry monitoring, ECG, non-invasive blood pressure measurement and the BIS are
38 started.
39

40 Preoxygenation takes place with a FiO_2 of 0.8 and a fresh gas flow of 7 l/min.
41

42 As soon as the BIS measurement starts, the BIS value and an initial blood pressure value is
43 noted.
44

45 If it is possible to establish i.v. access, an initial propofol bolus of 2-4 mg/kg body weight is
46 applied. The children are breathing spontaneously. When the oxygen saturation drops below
47 90%, a ventilation via a face mask takes place.
48

49 The schedule of interventions is also summarized in Figure 2.
50

51 IOP measurements take place during different depths of anaesthesia. Measurement is taken
52 by one experienced examiner per child (KM, AKS, EMH). A first IOP measurement is
53 performed when sufficient sedation for IOP measurement after titrated propofol application
54 (2-4 mg/kg or more if necessary) is achieved. A second IOP measurement is carried out 60 s
55 after placement of the laryngeal mask to avoid a potentially falsely high IOP value due to a
56 direct sympathicotonic reaction caused by the laryngeal mask placement. Then, a third IOP
57 measurement is taken after a break of 60 s directly after blockage of the cuff of the laryngeal
58 mask (60 cmH₂O).
59
60

IOP measurement of each eye is performed with the iCare® PRO tonometer followed by a measurement with the Perkins applanation tonometer after a one-minute waiting time to avoid potential influence of repetitive measurements on IOP.

Central corneal thickness (CCT) has an influence on IOP measurement in adults and children and is measured in this study.¹⁹ CCT has also been shown to be a relevant factor in the evaluation of childhood glaucoma in many studies and appears to result in significant differences in the measurement of IOP, depending on the device used.²⁰ This is why two different devices are used in this study. All IOP measurements are performed by one of three expert study investigators.

The Perkins Mk3 is available for measuring IOP. The Perkins Mk3 is a mobile, battery-powered applanation tonometer, which consists of the following components: a forehead support for correct placement, a handgrip for the examiner, a LED light source with a blue filter, a biprism and a force transducer. The force transducer measures how much force the examiner must use to flatten the cornea to a defined circular area of 4.8 mm² (diameter 3.06 mm). For the visualization of the edge of this surface, fluoresceine (a fluorescent dye) is applied in advance to the cornea. In compliant adults the awake patient is examined after topical application of a local anaesthetic.

The system draws on the 1965 prototype developed by Perkins.²¹ It has been specifically designed to measure IOP in patients who cannot adequately sit upright at a standard stationary applanation tonometer.

The iCare® ProTonometer (iCare Finland Oy, 01510 Vantaa, Finland, German distribution by bon Optic Vertriebsgesellschaft GmbH, Lübeck, Germany) has been available for in- and outpatient as well as self-tonometry since its certification in 2010. The iCare® PRO Tonometer is a mobile, battery-operated rebound or induction tonometer, which consists of the following components: a forehead support for correct placement, a handle for the examiner and a miniaturized measuring head. The measuring head bounces against the cornea from a short distance in six, very short individual measurements. Depending on the IOP, the measuring head is slowed down to varying degrees, from which the device calculates the IOP using magnetic coils. The compliant awake patient does not require local anaesthesia. Only a few studies have compared the two techniques in children.^{22 23}

The agreement between the instruments (Perkins applanation tonometry and iCare rebound tonometry) has been evaluated only in a few studies under different conditions than our study. Rebound tonometry has been shown to overestimate IOP in high IOP values.

Central corneal thickness measurement

Measurement of central corneal thickness is performed by Tomey AL-3000 (Tomey GmbH, Nurnberg, Germany). The SP-3000 is an ophthalmic diagnosis instrument which acquires corneal thickness, by using ultrasonic waves that are transmitted from the ultrasonic oscillator enclosed in the probe. One measurement is performed in each eye.

In addition to IOP measurements, BIS values, blood pressure (including mean arterial pressure), heart rate and oxygen saturation are documented for each time point of IOP measurement. General anaesthesia is maintained with a syringe pump of propofol at a rate of 4-5 mg/kg/h and a syringe pump of remifentanil with a running rate of 0.3 µg/kg/min. In case an i.v. access is initially not possible, mask induction of EUA via sevoflurane (4 vol%, flow 7 l/min, FiO₂ 0.8) is performed, followed by the establishment of an i.v. access.

Figure 3 presents all interventions on a time scale.

Bispectral Index Monitoring

The study uses the Aspect XP Bispectral Index Monitor (Medtronic Inc, Minneapolis, MN 55432, USA). It is available for intraclinical brain function monitoring by deriving raw EEG signals from patients for perioperative or intensive care monitoring, as well as for clinical research.

As described in the introduction, the BIS, with a dimension of 0-100, is a calculated EEG variable and can be used to aid in assessing the effects of anaesthetics. A BIS score below 60 indicates the degree of hypnosis of general anaesthesia. The measurement is carried out by a sensor fitted for the paediatric anatomy (BISTM Paediatric Sensor), which is mounted on the forehead of the patient.

Data from children who had to undergo mask induction are excluded from the main analysis and analyzed separately. Criteria to cancel the intervention include an unexpectedly difficult airway, an unrecoverable laryngeal mask leak, a different need for endotracheal intubation, and circulatory instability requiring intervention.

Outcomes measures

Primary outcome of the study is the correlation between Bispectral Index (BIS) and intraocular pressure (IOP) under standardised anaesthetic conditions.

Aim of this protocol paper is to report design and baseline characteristics of EyeBIS, a study to develop a standardised anaesthetic protocol for the measurement of IOP under general anaesthesia in childhood glaucoma by investigating the partial correlation between the magnitude of IOP and depth of anaesthesia adjusting for potential confounders.

Secondary outcome measures include the comparison of two different IOP measurements methods (applanation tonometry and rebound tonometry), the magnitude of the paediatric IOP during EUA in relation to cuff pressure of the laryngeal mask, regarding end expiratory CO₂ pressure, blood pressure and heart frequency, effect size of midazolam premedication and the definition of the normal range of the paediatric IOP, as well as the correlation of the CCT and IOP (determined by regression of IOP on CCT).

Primary and secondary outcomes are also shown in Figure 1.

Data collection, management and analysis

Data collection and management of the present study

For data collection, a paper-based case report form (CRF) was developed and is used for each patient. In addition to all other documentation, the CRF and the patient's study file belongs to the source data. The CRF contains information that is requested directly from the patient and thus cannot be verified on the basis of the patient's study file (screening information and data collected in the OR).

For pseudonymization purposes, every patient is coded with a specific patient number. In addition to the paper-based form, this study is also documented electronically. For this purpose, all information from the study file and the CRF are transferred to the computer in a tabular form.

Access to data

Data management of the present study is performed by the main investigator. All electronically stored data are backed up regularly. The pseudonymity of patients is ensured throughout the evaluation. All study data, including the electronically recorded data, will be

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3 archived and kept for at least 15 years after completion of the study according to the
4 currently valid ICH Guidelines on Good Clinical Practice (GCP) E6 (R2). Data are accessible
5 to all participating personnel and monitors. The database management system is capable of
6 producing accurate and complete copies of the data in visual form for inspection by
7 government agencies or ethics committees. Enrolled patients and their authorised
8 representative have been informed about this.
9

10 Monitoring

11 Prior to enrolling patients, the investigators were briefed on the CRF and study protocol. All
12 documents required for data collection are available in the operating theatre. Each CRF is
13 filled in by the investigator after the measurements have been performed. The data is then
14 promptly entered electronically under his supervision. The investigator regularly evaluates
15 the progress of data collection and study outcomes in order to address any emerging data
16 collection issues at an early stage. The data monitoring is managed and analysed in
17 accordance with the ICH GCP Guideline E6 (R2) and followed the requirements of German
18 Drug Law.
19

20
21 Adverse events will be recorded after patient enrolment. The study will be temporarily
22 interrupted by the attending investigator at any time on the individual subject, if a serious
23 adverse event is suspected, which may be associated with IOP measurement or an airway
24 device being used. A suspected adverse event or adverse reaction will be considered
25 serious when it comes to one of the following events: death, a life threatening reaction leading
26 to inpatient hospitalization, and a persistent or significant incapacity or substantial disability
27 of the normal age-adapted life functions. If the protocol is discontinued as a result of an
28 adverse event, study personnel will document the circumstances and data leading to the
29 discontinuation of measurement. The principal investigator will inform the local research
30 ethics committee (REC) in case of a severe adverse event following local standard operating
31 procedures.
32
33

34 The Clinical Research Unit of the Department of Anaesthesiology, University Center Mainz
35 inspects and reviews screening forms and clinical data at regular intervals.
36
37

38 Sample size considerations

39 With the envisaged number of 100 subjects, a single IOP measurement of one eye and
40 parallel determination of the BIS, the null hypothesis "correlation = 0" can be rejected in a
41 two-sided test at the 5% level with 86.5% power if the correlation amounts to 0.3. If the actual
42 correlation is 0.35, the power rises to 95%. The multiple measurements provide additional
43 information, resulting in a power gain. It is not yet possible to anticipate how strong the
44 correlation between the multiple measurements will be. With decreasing correlation between
45 repeat measurements power increases and, similarly, also smaller correlation between IOP
46 and BIS will be detectable for fixed power – how small depends on the yet unknown
47 correlations.
48

49 For statistical analysis, SAS statistical software will be used. The analysis corresponds to
50 STROBE statement for observational studies.
51
52
53

54 Description of patient group at baseline

55
56 The baseline features of patients will be described using absolute numbers (n) and
57 percentages for categorical variables and the minimum, maximum, mean and standard
58 deviation for normally distributed variable and as median (IQR) for non-Gaussian variables.
59 The Pearson correlation coefficient will be used to compare patient specifics between the
60 groups and the baseline.

Analysis of the primary outcome

The relationship between the IOP and BIS will be investigated using a mixed linear model including measurements at all three time points. In this model, IOP is the dependent variable, the BIS is the main independent variable. Random effects are subject and eye (of a subject). Time per se is not of interest as essentially the depth of anaesthesia measured by BIS at each time point is of interest. Time will be considered by taking repeated measurements into account. Further, we will adjust for age (quantitative), sex, CCT, and cumulative midazolam dose administered until the time of measurement) Eyes within a patient are likely not to be independent, therefore a random patient effect is included in the model.

Analysis of the secondary outcome

To compare the two measurement methods for IOP, applanation tonometry and rebound tonometry, Bland-Altman diagrams will be created.

The dependence of IOP under general anaesthesia on the cuff pressure of the laryngeal mask, the end tidal CO₂ partial pressure, the blood pressure and the heart rate will also be described by a mixed linear model, with the variables mentioned above as covariates and random effects for subject and eye and adjustment for corneal thickness. The general considerations for the primary outcome apply here, too.

For children without glaucoma, a quantile regression will be performed that takes into account the factors mentioned above. From this, it is possible to deduce standard ranges in which e.g. 90% or 95% of the values of healthy children are expected.

Subgroup analysis

Data from children who had to undergo mask induction will be analyzed separately.

DISCUSSION

Several studies have documented various variables that have an impact on the paediatric IOP [3]. The weakness of the previously published studies is that none has examined all in a single study setting. To our current knowledge, the EyeBIS study is the only clinical study of its kind to associate IOP in 100 childhood glaucoma patients and 20 non-glaucoma patients (control group) with the depth of anaesthesia under the best possible standardized environmental conditions. Due to the exclusivity and safety of our patient population.

In conclusion, if our study will find a partial correlation between BIS and IOP this could lead to more reliable IOP data in childhood glaucoma examinations under anaesthesia. This protocol could be a reference standard for children with suspected glaucoma who cannot undergo an examination while awake. This leads to an improved, more reliable ability to diagnose glaucoma with an earlier therapy, which overall leads to a significantly better functional outcome for children.

ETHICS AND DISSEMINATION

Research ethics approval

The requirements of the ICH Guideline for Good Clinical Practice (GCP) E6 of June 1996 and of CPMP/ICH/135/95 of September 1997 are, in addition to the national laws and the Declaration of Helsinki (Somerset West 1996), the basis for carrying out this study.

All study personnel are obliged to participate in this study according to these guidelines.

Consent or assent

Before being included in the study, the study will be verbally and comprehensibly explained to patient and one of his/her authorized representatives by a clinical study investigator, as required by German law. He/she will also receive a comprehensively written information

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3 sheet. The authorized representatives will have the opportunity to have an informed
4 discussion with the clinical study investigator about the study.
5

6 The clinical study investigator will obtain written consent from the authorized representatives
7 willing to participate in the trial. The information leaflet and a new execution of the consent
8 document will be handed over to one of the authorized representatives. Upon request, the
9 patient will receive a child-friendly version of the information leaflet.
10

11 The authorised representative may withdraw from the study at any time if he/she is unwilling
12 to continue in the trial. In this case, the data from a patient who requests full withdrawal will
13 not be considered in the data analysis.
14

15 **Confidentiality**

16 All original documents will be kept in the clinical research unit for the next 15 years. The
17 study data will be handled as requested by the German Federal Data Protection Act, which
18 implements the Directive 95/46/EC on data protection (Data Protection Directive). All original
19 records will be kept on file at the trial sites or coordinating data managing centre for 15 years.
20 The cleaned electronic trial database file will be anonymized and kept on file for 15 years.
21

22 **Acknowledgements**

23
24
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26 Anaesthesiology and Ophthalmology for their great effort and support for this study. They
27 also thank Patricia Buchholz RPh, PhD for writing support.
28

29 **Author contributions**

30
31 The study concept and design were conceived by NP, EMH, KM, IS and EW. NP, EMH and
32 KM are conducting screening and data collection. Analysis and interpretation of data will be
33 performed by IS, EW, NP, EMH, KM, FG and AKS.
34

35 KM and NP prepared the first draft of the manuscript. All (NP, FG, EMH, KM, IS, EW, AKS,
36 KM) authors have provided edits and critiqued the manuscript for intellectual content, as well
37 as have given final approval for manuscript submission. Results of this study will be part of
38 the doctoral thesis of KM.
39
40

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42
43
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45 profit).
46

47 **Declaration of interests**

48
49 Neither the University Medical Centre of the Johannes Gutenberg University, Mainz, nor its
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55 played no part in the funding, design, conduct, evaluation or publication of this study.
56

57 **Provenance and peer review**

58
59 Not commissioned; externally peer reviewed.
60

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11 granted.
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13 The results of this study will be presented at conferences and published in peer reviewed
14 journals
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3 **Figure captions**
4

5 Figure 1:

6 Study flow chart according to American Society of Anaesthesiologists (ASA) with inclusion
7 and exclusion criteria, as well as outcome measures
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9
10 Figure 2:

11 Schedule of study enrolment and interventions. i.v., intravenous; SpO₂, oxygen saturation;
12 ECG, electrocardiography; BIS, bispectral index; IOP, intraocular pressure.
13

14 Figure 3:

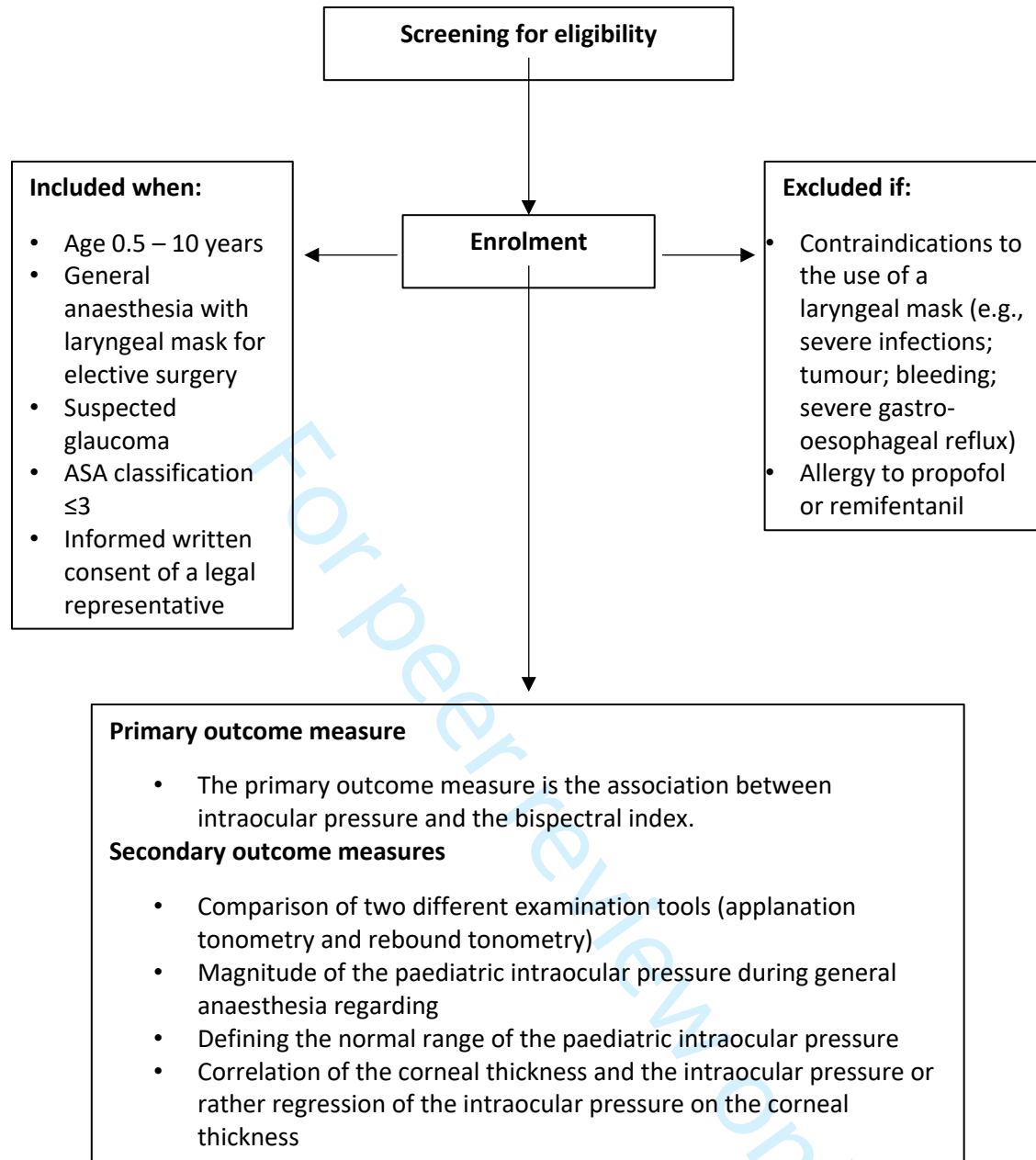
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16 EyeBIS worksheet. Detailed layout of all steps on the interventional time scale
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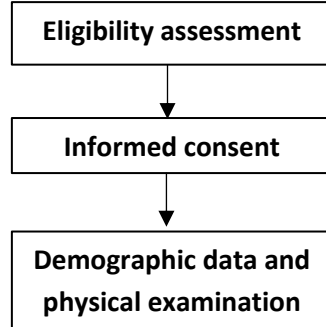
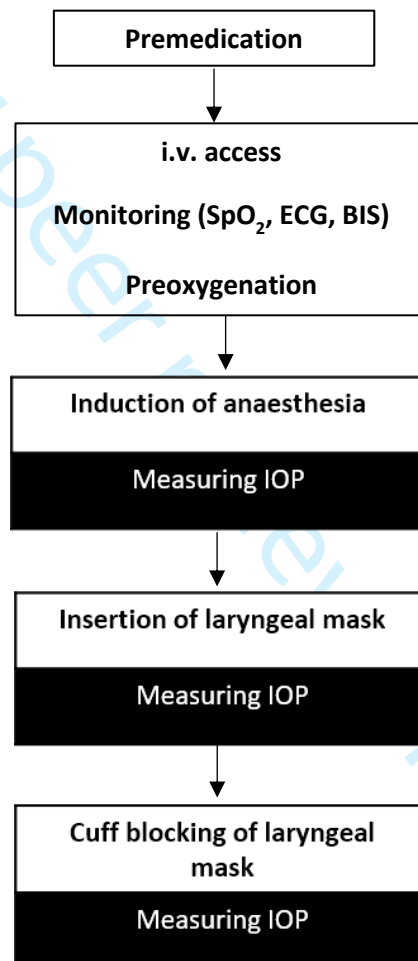
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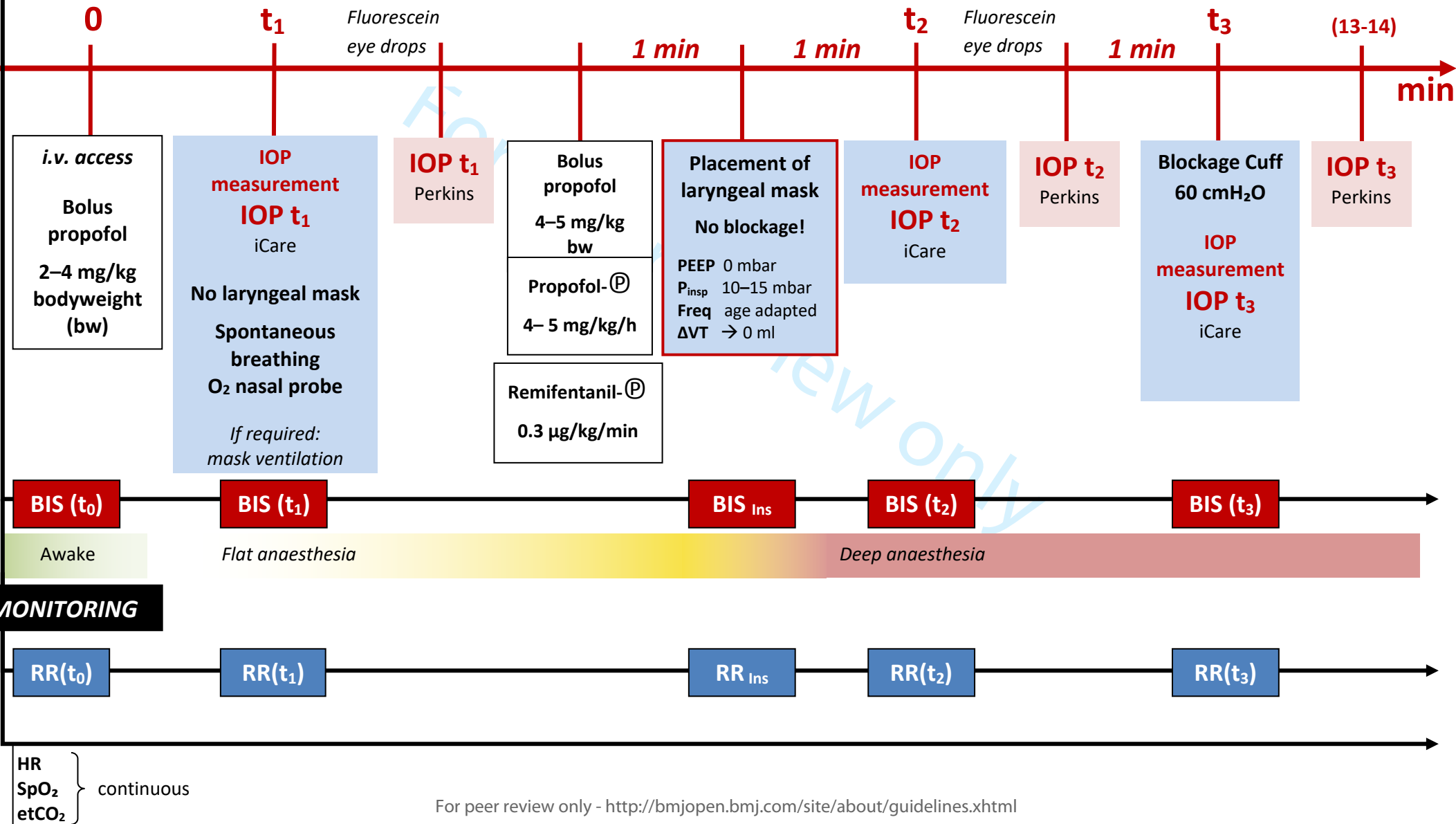


eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

$FiO_2 = 0.8$
Fresh gas flow 7 l/min



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

1	Roles and	#5b	Name and contact information for the trial sponsor	11
2	responsibilities:			
3	sponsor contact			
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8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	11
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
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16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	11
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
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23				
24	Introduction			
25				
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27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms for	
30			each intervention	
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34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
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39	Objectives	#7	Specific objectives or hypotheses	4
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
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48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
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54				
55	Study setting	#9	Description of study settings (eg, community clinic, academic	5
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
7	description			
8				
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10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
11	modifications			
12				
13				
14				
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17	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
18	adherence			
19				
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22	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
23	concomitant care			
24				
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26	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
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37	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
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43	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
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48	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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Methods:

Assignment of interventions (for controlled trials)

1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	n/a
2	generation			
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10	Allocation	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	n/a
11	concealment			
12	mechanism			
13				
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17	Allocation:	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	5
18	implementation			
19				
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21	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	n/a
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26	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	n/a
27	emergency unblinding			
28				
29				
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32	Methods: Data			
33	collection,			
34	management, and			
35	analysis			
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39	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	8
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50	Data collection plan:	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
51	retention			
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57	Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data	8
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entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

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5	Statistics: outcomes	#20a	9
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11	Statistics: additional analyses	#20b	9
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15	Statistics: analysis population and missing data	#20c	9
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20	Methods: Monitoring		
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22	Data monitoring: formal committee	#21a	8
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32	Data monitoring: interim analysis	#21b	n/a
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37	Harms	#22	9
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43	Auditing	#23	9
44			
45			
46			
47			
48	Ethics and dissemination		
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52	Research ethics approval	#24	5
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56	Protocol amendments	#25	n/a
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relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

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4	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
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9	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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14	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
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20	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site
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24	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
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29	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
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34	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
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43	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers
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47	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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Appendices

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53	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates
54			
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57	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the
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1 current trial and for future use in ancillary studies, if
2 applicable
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5 3.0. This checklist was completed on 14. September 2020 using <https://www.goodreports.org/>, a tool made by
6 the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS study protocol

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5 **Anaesthetic protocol for paediatric glaucoma examinations - the prospective EyeBIS**
6 **study protocol**
7

8
9 Nina Pirlich¹, Franz Grehn³, Katja Mohnke¹, Konrad Maucher¹, Alexander K.
10 Schuster³, Eva Wittenmeier¹, Irene Schmidtman², Esther M. Hoffmann³
11

12 ¹Department of Anaesthesiology, University Medical Centre of the Johannes Gutenberg-
13 University Mainz, Mainz, Germany

14 ² Institute of Medical Biostatistics, Epidemiology and Informatics, University Medical Centre
15 of the Johannes Gutenberg-University Mainz, Mainz, Germany

16 ³Department of Ophthalmology, University Medical Centre of the Johannes Gutenberg-
17 University Mainz, Mainz, Germany
18
19
20
21

22
23 Correspondence to:
24 Esther M. Hoffmann
25 Augenklinik und Poliklinik
26 Universitätsmedizin Mainz
27 Langenbeckstr. 1
28 55131 Mainz
29 Fax: +496131176620
30 Phone: +496131177085
31

32 ehoffman@uni-mainz.de
33
34
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ABSTRACT

Introduction Neonates and young infants with diagnosed or highly suspected glaucoma require an examination under anaesthesia to achieve accurate intraocular pressure (IOP) measurements, since crying or squinting of the eyes may increase IOP and lead to falsely high values. IOP considerably depends on perioperative variables such as haemodynamic factors, anaesthetics, depth of anaesthesia and airway management. The aim of this paper is to report the design and baseline characteristics of EyeBIS, which is a study to develop a standardized anaesthetic protocol for the measurement of IOP under anaesthesia in childhood glaucoma by investigating the link between the magnitude of IOP and depth of anaesthesia.

Methods and analysis This is a single centre, prospective cohort study in 100 children with diagnosed or highly suspected glaucoma all undergoing ophthalmological examination under general anaesthesia. 20 children, who undergo general anaesthesia for other reasons, are included as controls. The primary outcome measure is the establishment of a standardized anaesthetic protocol for IOP measurement in childhood glaucoma by assessing the relationship between IOP and depth of anaesthesia (calculated as an electroencephalography (EEG) variable, the bispectral index (BIS)), with special emphasis on airway management and haemodynamic parameters. The dependence of IOP under anaesthesia on airway management and haemodynamic parameters will be described, using a mixed linear model. Restricting the model to patients with healthy eyes, will allow to determine a 95% reference region, in which 95% of the measurement values of patients with healthy eyes can be expected.

Ethics and dissemination The study has been approved by the local ethics committee of the Medical Association of Rhineland-Palatine (Ethik-Kommission der Landesärztekammer Rheinland-Pfalz), Germany (Approval number: 2019-14207). This work will be disseminated by publication of peer-reviewed manuscripts, presentation in abstract form at national and international scientific meetings and data sharing with other investigators.

Trial registration number ClinicalTrials.gov NCT03972852

Key words: glaucoma, children, intraocular pressure, anaesthesia, standard protocol

STRENGTHS AND LIMITATIONS OF THIS STUDY

- EyeBIS will be the first study investigating the measurement of IOP in neonates and young infants taking into account the complexity of multifactorial disruptive perioperative factors.
- EyeBIS will provide data on distribution of paediatric intraocular pressure.
- The developed protocol may provide a recommendation for other glaucoma centres.
- It is only a single-centre observational study.

For peer review only

INTRODUCTION

Background and rationale

A basic requirement for diagnosis, monitoring and therapy of childhood glaucoma is the accurate measurement of intraocular pressure (IOP). Despite newer less invasive measurement techniques (rebound technology), neonates and young infants still require an examination under anaesthesia (EUA), either under sedation or general anaesthesia.

Squinting and the elevated stress level following the release of catecholamines may lead to falsely high IOP values and subsequently to inadequate therapy. Success rates for correct measurement of IOP in awake children vary between 14% and 60% in the literature.^{1 2} As congenital glaucoma damage in newborns and young children is exclusively intraocular pressure (IOP) related (i.e. Descemet tears, optic nerve head damage) accurate measurement of IOP under EUA is crucial.

To date, there are no prospective studies from which detailed recommendations on standardized general anaesthesia in children with glaucoma may be derived.

Perioperative anaesthetics include all inhalation anaesthetics and most centrally depressing drugs such as propofol, benzodiazepines and opioids. They result in a reduction of IOP in both healthy and glaucomatous eyes.³ The depth of anaesthesia and IOP reduction are correlated. IOP-lowering effects depend on the applied dose and on the time of administration⁴⁻⁷. The effects of propofol on IOP are mainly known in adult patients, where IOP reduction is suspected to be associated with the lowering of the mean arterial pressure.⁸ Available data on the effect of propofol on IOP in healthy children is inconsistent and there are no data in children with glaucoma.⁹ Furthermore, there are no data on the influence of opioids on the IOP of children with glaucoma.

When applying anaesthesia, airway management also has an influence on IOP.³ Laryngoscopy and intubation can increase IOP substantially, especially when it comes to coughing. However, IOP may rise even without an externally detectable reaction such as a sympathicotonic cardiovascular mechanism, especially with shallow anaesthesia.¹⁰⁻¹² Laryngeal masks are widely used in adult and paediatric respiratory management and considered safe by paediatric anaesthesiologists in a variety of clinical settings.¹³ Compared to endotracheal intubation in children, the use of laryngeal masks is associated with less cardiovascular reactions and a lesser increase in IOP.¹⁴

The EyeBIS study will be the first study to employ a strict standardized protocol for anaesthesia in children with glaucoma. The study will assess the relationship between depth of anaesthesia and IOP in this population. To determine depth of anaesthesia, the bispectral index (BIS) is used. The index has a range of 0-100 and is a calculated electroencephalography (EEG) variable, used to measure the effects of anaesthetics. A BIS score below 60 indicates the degree of hypnosis of EUA. Both Schäfer and Hanna have described the need to investigate the relationship between depth of anaesthesia and IOP.^{6 15} A correlation between IOP and depth of anaesthesia using BIS in children is already available.¹⁶ The purpose of this manuscript is to report on this protocol in the population described below.

METHODS AND ANALYSIS

Study setting and design

The Department of Ophthalmology, University Medical Center Mainz, has developed an expertise in childhood glaucoma diseases. In the years 2016 and 2017, surgery was performed in approximately 80 children. Since the founding of the German Childhood Glaucoma Centre at the University Medical Center Mainz in June 2017, the number of children receiving a glaucoma diagnosis or surgery has increased significantly. The collaboration between paediatric ophthalmologists and paediatric anaesthesiologists has led to an enhanced focus and expertise in this area and identified the necessity to develop a standardized protocol for general anaesthesia while performing IOP measurements. Established and safe anaesthesia regimens have been modified, taking into account various known factors that influence the measurement of IOP.

With the planned study, we would like to evaluate whether reliable and reproducible measurement values can be generated by a standardized protocol. The EyeBIS trial is a prospective, single-centre, non-randomized clinical trial.

Patient and Public Involvement

Patients of this research were first involved in June 2019 by the research team (NP and EMH, and medical students). Eligible patients (see section below) were asked whether they are interested in this study. Inclusion criteria were discussed with parents and children and patients were examined according to the individual standards and SOPs of the Clinic for Anaesthesiology and the Dept. of Ophthalmology. Patients were not involved in the development and design of the study protocol. The public was not involved. Study results will not be disseminated to participants specifically. However, if participants are interested in the results of the research they will receive any information, the manuscript, and published research on this topic in the future.

Trial population and eligibility criteria

Children in the age group 6 months to 10 years will be included, when meeting the following criteria: requirement of EUA with a laryngeal mask for a surgical or diagnostic procedure; suspected glaucoma or control children undergoing ocular surgery other than glaucoma surgery (control group); ASA classification 1, 2 or 3; and informed written consent from one of their legal representatives.

Patients will not be included in this trial if they meet one or more of the following criteria: contraindications to the use of a laryngeal mask (e.g., severe infections; tumour or bleeding in the upper airway tract, which might prevent the sufficient placement of the laryngeal mask; if the expected magnitude of ventilation pressure exceeds the upper leakage pressure of the laryngeal mask (40 cm H₂O); the necessity of a constant tracheal access; patients with a severe gastro-oesophageal reflux; or interference of the laryngeal mask with the surgical approach), or known allergy to propofol or remifentanyl. Eligibility criteria are shown in Figure 1.

Recruitment and participant timelines

Participant inclusion started in June 2019 in the Childhood Glaucoma Centre at the University Medical Centre, Mainz, Germany. The history and physical examinations of all patients scheduled for surgery were screened preoperatively for predictors of difficult airway, oesophageal reflux and allergies.

Patient will be informed about the study by the investigators and medical students (EMH, NP) Patients will be included if they require the insertion of a laryngeal mask under general

1
2
3 anaesthesia. Informed consent for all paediatric participants will be obtained from one of their
4 legal representatives. This also includes information and consent according to the German
5 Medical Privacy Rules (DSGVO, in analogy to the US Insurance Portability and
6 Accountability Act of 1996 (HIPAA)). Prospective approval of the study will be granted by the
7 local ethics committee of the Medical Association of the Rhineland-Palatine state (Ethik-
8 Kommission der Landesärztekammer Rheinland-Pfalz), Germany (approval number: 2019-
9 14207). The Clinical Trials registration number of the study is ClinicalTrials.gov
10 NCT03972852.
11

12
13 The schedule of study enrolment is shown in Figure 2.
14

15 16 **Intervention**

17 Induction and maintenance of EUA is performed. In the present study, the laryngeal mask
18 Ambu® AuraGain™ (German distribution by Ambu GmbH, Bad Nauheim, Germany) is used,
19 which is a second-generation laryngeal mask with integrated gastric access and the
20 possibility of fiberoptic intubation.¹⁷ Compression of the cervical vessels through the cuff of
21 laryngeal masks has been reported in adults.¹⁸ It has not been investigated whether the
22 blockage of a laryngeal mask in children has an influence on IOP by obstructing the venous
23 return. According to the standard operating procedures of the Department of
24 Anaesthesiology, a premedication with oral midazolam (juice) is administered when the
25 patient is collected from the ward. A dosage of 0.5 mg/kg (up to a maximum dose of 10 mg)
26 is given.
27
28

29 Local anaesthetics are applied topically to two possible puncture sites at least 1 h prior to
30 surgery. Before induction of anaesthesia, intravenous (i.v.) access is established. The child's
31 head is positioned in a neutral way in a head ring, with the body in a flat back position. To
32 optimize mask ventilation, the shoulder blades are padded with a rolled-up surgical tissue.
33
34

35 The induction and maintenance of EUA is performed by an anaesthesiologist, specifically
36 educated in anaesthesia for neonates and young infants. Before initiating the EUA, pulse
37 oximetry monitoring, ECG, non-invasive blood pressure measurement and the BIS are
38 started.
39

40 Preoxygenation takes place with a FiO_2 of 0.8 and a fresh gas flow of 7 l/min.
41

42 As soon as the BIS measurement starts, the BIS value and an initial blood pressure value is
43 noted.
44

45 If it is possible to establish i.v. access, an initial propofol bolus of 2-4 mg/kg body weight is
46 applied. The children are breathing spontaneously. When the oxygen saturation drops below
47 90%, a ventilation via a face mask takes place.
48

49 The schedule of interventions is also summarized in Figure 2.
50

51 IOP measurements take place during different depths of anaesthesia. Measurement is taken
52 by one experienced examiner per child (KM, AKS, EMH). A first IOP measurement is
53 performed when sufficient sedation for IOP measurement after titrated propofol application
54 (2-4 mg/kg or more if necessary) is achieved. A second IOP measurement is carried out 60 s
55 after placement of the laryngeal mask to avoid a potentially falsely high IOP value due to a
56 direct sympathicotonic reaction caused by the laryngeal mask placement. Then, a third IOP
57 measurement is taken after a break of 60 s directly after blockage of the cuff of the laryngeal
58 mask (60 cmH_2O).
59
60

IOP measurement of each eye is performed with the iCare® PRO tonometer followed by a measurement with the Perkins applanation tonometer after a one-minute waiting time to avoid potential influence of repetitive measurements on IOP.

Central corneal thickness (CCT) has an influence on IOP measurement in adults and children and is measured in this study.¹⁹ CCT has also been shown to be a relevant factor in the evaluation of childhood glaucoma in many studies and appears to result in significant differences in the measurement of IOP, depending on the device used.²⁰ This is why two different devices are used in this study. All IOP measurements are performed by one of three expert study investigators.

The Perkins Mk3 is available for measuring IOP. The Perkins Mk3 is a mobile, battery-powered applanation tonometer, which consists of the following components: a forehead support for correct placement, a handgrip for the examiner, a LED light source with a blue filter, a biprism and a force transducer. The force transducer measures how much force the examiner must use to flatten the cornea to a defined circular area of 4.8 mm² (diameter 3.06 mm). For the visualization of the edge of this surface, fluoresceine (a fluorescent dye) is applied in advance to the cornea. In compliant adults the awake patient is examined after topical application of a local anaesthetic.

The system draws on the 1965 prototype developed by Perkins.²¹ It has been specifically designed to measure IOP in patients who cannot adequately sit upright at a standard stationary applanation tonometer.

The iCare® ProTonometer (iCare Finland Oy, 01510 Vantaa, Finland, German distribution by bon Optic Vertriebsgesellschaft GmbH, Lübeck, Germany) has been available for in- and outpatient as well as self-tonometry since its certification in 2010. The iCare® PRO Tonometer is a mobile, battery-operated rebound or induction tonometer, which consists of the following components: a forehead support for correct placement, a handle for the examiner and a miniaturized measuring head. The measuring head bounces against the cornea from a short distance in six, very short individual measurements. Depending on the IOP, the measuring head is slowed down to varying degrees, from which the device calculates the IOP using magnetic coils. The compliant awake patient does not require local anaesthesia. Only a few studies have compared the two techniques in children.^{22 23}

The agreement between the instruments (Perkins applanation tonometry and iCare rebound tonometry) has been evaluated only in a few studies under different conditions than our study. Rebound tonometry has been shown to overestimate IOP in high IOP values.

Central corneal thickness measurement

Measurement of central corneal thickness is performed by Tomey AL-3000 (Tomey GmbH, Nurnberg, Germany). The SP-3000 is an ophthalmic diagnosis instrument which acquires corneal thickness, by using ultrasonic waves that are transmitted from the ultrasonic oscillator enclosed in the probe. One measurement is performed in each eye.

In addition to IOP measurements, BIS values, blood pressure (including mean arterial pressure), heart rate and oxygen saturation are documented for each time point of IOP measurement. General anaesthesia is maintained with a syringe pump of propofol at a rate of 4-5 mg/kg/h and a syringe pump of remifentanil with a running rate of 0.3 µg/kg/min. In case an i.v. access is initially not possible, mask induction of EUA via sevoflurane (4 vol%, flow 7 l/min, FiO₂ 0.8) is performed, followed by the establishment of an i.v. access.

Figure 3 presents all interventions on a time scale.

Bispectral Index Monitoring

The study uses the Aspect XP Bispectral Index Monitor (Medtronic Inc, Minneapolis, MN 55432, USA). It is available for intraclinical brain function monitoring by deriving raw EEG signals from patients for perioperative or intensive care monitoring, as well as for clinical research.

As described in the introduction, the BIS, with a dimension of 0-100, is a calculated EEG variable and can be used to aid in assessing the effects of anaesthetics. A BIS score below 60 indicates the degree of hypnosis of general anaesthesia. The measurement is carried out by a sensor fitted for the paediatric anatomy (BISTM Paediatric Sensor), which is mounted on the forehead of the patient.

Data from children who had to undergo mask induction are excluded from the main analysis and analyzed separately. Criteria to cancel the intervention include an unexpectedly difficult airway, an unrecoverable laryngeal mask leak, a different need for endotracheal intubation, and circulatory instability requiring intervention.

Outcomes measures

Primary outcome of the study is the correlation between Bispectral Index (BIS) and intraocular pressure (IOP) under standardised anaesthetic conditions.

Aim of this protocol paper is to report design and baseline characteristics of EyeBIS, a study to develop a standardised anaesthetic protocol for the measurement of IOP under general anaesthesia in childhood glaucoma by investigating the partial correlation between the magnitude of IOP and depth of anaesthesia adjusting for potential confounders.

Secondary outcome measures include the comparison of two different IOP measurements methods (applanation tonometry and rebound tonometry), the magnitude of the paediatric IOP during EUA in relation to cuff pressure of the laryngeal mask, regarding end expiratory CO₂ pressure, blood pressure and heart frequency, effect size of midazolam premedication and the definition of the normal range of the paediatric IOP, as well as the correlation of the CCT and IOP (determined by regression of IOP on CCT).

Primary and secondary outcomes are also shown in Figure 1.

Data collection, management and analysis

Data collection and management of the present study

For data collection, a paper-based case report form (CRF) was developed and is used for each patient. In addition to all other documentation, the CRF and the patient's study file belongs to the source data. The CRF contains information that is requested directly from the patient and thus cannot be verified on the basis of the patient's study file (screening information and data collected in the OR).

For pseudonymization purposes, every patient is coded with a specific patient number. In addition to the paper-based form, this study is also documented electronically. For this purpose, all information from the study file and the CRF are transferred to the computer in a tabular form.

Access to data

Data management of the present study is performed by the main investigator. All electronically stored data are backed up regularly. The pseudonymity of patients is ensured throughout the evaluation. All study data, including the electronically recorded data, will be

1
2
3 archived and kept for at least 15 years after completion of the study according to the
4 currently valid ICH Guidelines on Good Clinical Practice (GCP) E6 (R2). Data are accessible
5 to all participating personnel and monitors. The database management system is capable of
6 producing accurate and complete copies of the data in visual form for inspection by
7 government agencies or ethics committees. Enrolled patients and their authorised
8 representative have been informed about this.
9

10 Monitoring

11 Prior to enrolling patients, the investigators were briefed on the CRF and study protocol. All
12 documents required for data collection are available in the operating theatre. Each CRF is
13 filled in by the investigator after the measurements have been performed. The data is then
14 promptly entered electronically under his supervision. The investigator regularly evaluates
15 the progress of data collection and study outcomes in order to address any emerging data
16 collection issues at an early stage. The data monitoring is managed and analysed in
17 accordance with the ICH GCP Guideline E6 (R2) and followed the requirements of German
18 Drug Law.
19

20
21 Adverse events will be recorded after patient enrolment. The study will be temporarily
22 interrupted by the attending investigator at any time on the individual subject, if a serious
23 adverse event is suspected, which may be associated with IOP measurement or an airway
24 device being used. A suspected adverse event or adverse reaction will be considered
25 serious when it comes to one of the following events: death, a life threatening reaction leading
26 to inpatient hospitalization, and a persistent or significant incapacity or substantial disability
27 of the normal age-adapted life functions. If the protocol is discontinued as a result of an
28 adverse event, study personnel will document the circumstances and data leading to the
29 discontinuation of measurement. The principal investigator will inform the local research
30 ethics committee (REC) in case of a severe adverse event following local standard operating
31 procedures.
32
33

34 The Clinical Research Unit of the Department of Anaesthesiology, University Center Mainz
35 inspects and reviews screening forms and clinical data at regular intervals.
36
37

38 Sample size considerations

39 With the envisaged number of 100 subjects, a single IOP measurement of one eye and
40 parallel determination of the BIS, the null hypothesis "correlation = 0" can be rejected in a
41 two-sided test at the 5% level with 86.5% power if the correlation amounts to 0.3. If the actual
42 correlation is 0.35, the power rises to 95%. The multiple measurements provide additional
43 information, resulting in a power gain. It is not yet possible to anticipate how strong the
44 correlation between the multiple measurements will be. With decreasing correlation between
45 repeat measurements power increases and, similarly, also smaller correlation between IOP
46 and BIS will be detectable for fixed power – how small depends on the yet unknown
47 correlations. For the control group, we selected 20 children, having feasibility in mind. We
48 will, however, include further children in this group.
49
50
51

52 For statistical analysis, SAS statistical software will be used. The analysis corresponds to
53 STROBE statement for observational studies.
54
55
56

57 Description of patient group at baseline

58 The baseline features of patients will be described using absolute numbers (n) and
59 percentages for categorical variables and the minimum, maximum, mean and standard
60 deviation for normally distributed variable and as median (IQR) for non-Gaussian variables.

1
2
3 The Pearson correlation coefficient will be used to compare patient specifics between the
4 groups and the baseline.
5

6 **Analysis of the primary outcome**

7
8 The relationship between the IOP and BIS will be investigated using a mixed linear model
9 including measurements at all three time points. In this model, IOP is the dependent variable,
10 the BIS is the main independent variable. Random effects are subject and eye (of a subject).
11 Time per se is not of interest as essentially the depth of anaesthesia measured by BIS at
12 each time point is of interest. Time will be considered by taking repeated measurements into
13 account. Further, we will adjust for age (quantitative), sex, CCT, and cumulative midazolam
14 dose administered until the time of measurement) Eyes within a patient are likely not to be
15 independent, therefore a random patient effect is included in the model.
16

17 **Analysis of the secondary outcome**

18
19 To compare the two measurement methods for IOP, applanation tonometry and rebound
20 tonometry, Bland-Altman diagrams will be created.

21 The dependence of IOP under general anaesthesia on the cuff pressure of the laryngeal
22 mask, the end tidal CO₂ partial pressure, the blood pressure and the heart rate will also be
23 described by a mixed linear model, with the variables mentioned above as covariates and
24 random effects for subject and eye and adjustment for corneal thickness. The general
25 considerations for the primary outcome apply here, too.

26 For children without glaucoma, a quantile regression will be performed that takes into
27 account the factors mentioned above. From this, it is possible to deduce standard ranges in
28 which e.g. 90% or 95% of the values of healthy children are expected.
29

30 **Subgroup analysis**

31
32 Data from children who had to undergo mask induction will be analyzed separately.
33

34 **DISCUSSION**

35 Several studies have documented various variables that have an impact on the paediatric
36 IOP [3]. The weakness of the previously published studies is that none has examined all in a
37 single study setting. To our current knowledge, the EyeBIS study is the only clinical study of
38 its kind to associate IOP in 100 childhood glaucoma patients and 20 non-glaucoma patients
39 (control group) with the depth of anaesthesia under the best possible standardized
40 environmental conditions. Due to the exclusivity and safety of our patient population.
41

42
43 In conclusion, if our study will find a partial correlation between BIS and IOP this could lead
44 to more reliable IOP data in childhood glaucoma examinations under anaesthesia. This
45 protocol could be a reference standard for children with suspected glaucoma who cannot
46 undergo an examination while awake. This leads to an improved, more reliable ability to
47 diagnose glaucoma with an earlier therapy, which overall leads to a significantly better
48 functional outcome for children.
49

50 **ETHICS AND DISSEMINATION**

51 **Research ethics approval**

52
53 The requirements of the ICH Guideline for Good Clinical Practice (GCP) E6 of June 1996
54 and of CPMP/ICH/135/95 of September 1997 are, in addition to the national laws and the
55 Declaration of Helsinki (Somerset West 1996), the basis for carrying out this study.
56

57
58 All study personnel are obliged to participate in this study according to these guidelines.
59
60

Consent or assent

Before being included in the study, the study will be verbally and comprehensibly explained to patient and one of his/her authorized representatives by a clinical study investigator, as required by German law. He/she will also receive a comprehensively written information sheet. The authorized representatives will have the opportunity to have an informed discussion with the clinical study investigator about the study.

The clinical study investigator will obtain written consent from the authorized representatives willing to participate in the trial. The information leaflet and a new execution of the consent document will be handed over to one of the authorized representatives. Upon request, the patient will receive a child-friendly version of the information leaflet.

The authorised representative may withdraw from the study at any time if he/she is unwilling to continue in the trial. In this case, the data from a patient who requests full withdrawal will not be considered in the data analysis.

Confidentiality

All original documents will be kept in the clinical research unit for the next 15 years. The study data will be handled as requested by the German Federal Data Protection Act, which implements the Directive 95/46/EC on data protection (Data Protection Directive). All original records will be kept on file at the trial sites or coordinating data managing centre for 15 years. The cleaned electronic trial database file will be anonymized and kept on file for 15 years.

Acknowledgements

The authors would like to thank all involved doctors and nurses of the Department of Anaesthesiology and Ophthalmology for their great effort and support for this study. They also thank Patricia Buchholz RPh, PhD for writing support.

Author contributions

The study concept and design were conceived by NP, EMH, KM, IS and EW. NP, EMH and KM are conducting screening and data collection. Analysis and interpretation of data will be performed by IS, EW, NP, EMH, KM, FG and AKS.

KM and NP prepared the first draft of the manuscript. All (NP, FG, EMH, KM, IS, EW, AKS, KM) authors have provided edits and critiqued the manuscript for intellectual content, as well as have given final approval for manuscript submission. Results of this study will be part of the doctoral thesis of KM.

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Declaration of interests

Neither the University Medical Centre of the Johannes Gutenberg University, Mainz, nor its employees received any compensation for this study. There is no externally generated funding or competing interests. None of the authors has indicated financial interests or paid fees received in the course of this study. None of the authors has a personal relationship with companies, organizations or individuals that could interfere with this work in an inappropriate manner. Perkins, iCare, Ambu, 3M and Medtronic, whose products are included in this study, played no part in the funding, design, conduct, evaluation or publication of this study.

Provenance and peer review

Not commissioned; externally peer reviewed.

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The results of this study will be presented at conferences and published in peer reviewed journals

Figure captions

Figure 1:

Study flow chart according to American Society of Anaesthesiologists (ASA) with inclusion and exclusion criteria, as well as outcome measures

Figure 2:

Schedule of study enrolment and interventions. i.v., intravenous; SpO₂, oxygen saturation; ECG, electrocardiography; BIS, bispectral index; IOP, intraocular pressure.

Figure 3:

EyeBIS worksheet. Detailed layout of all steps on the interventional time scale

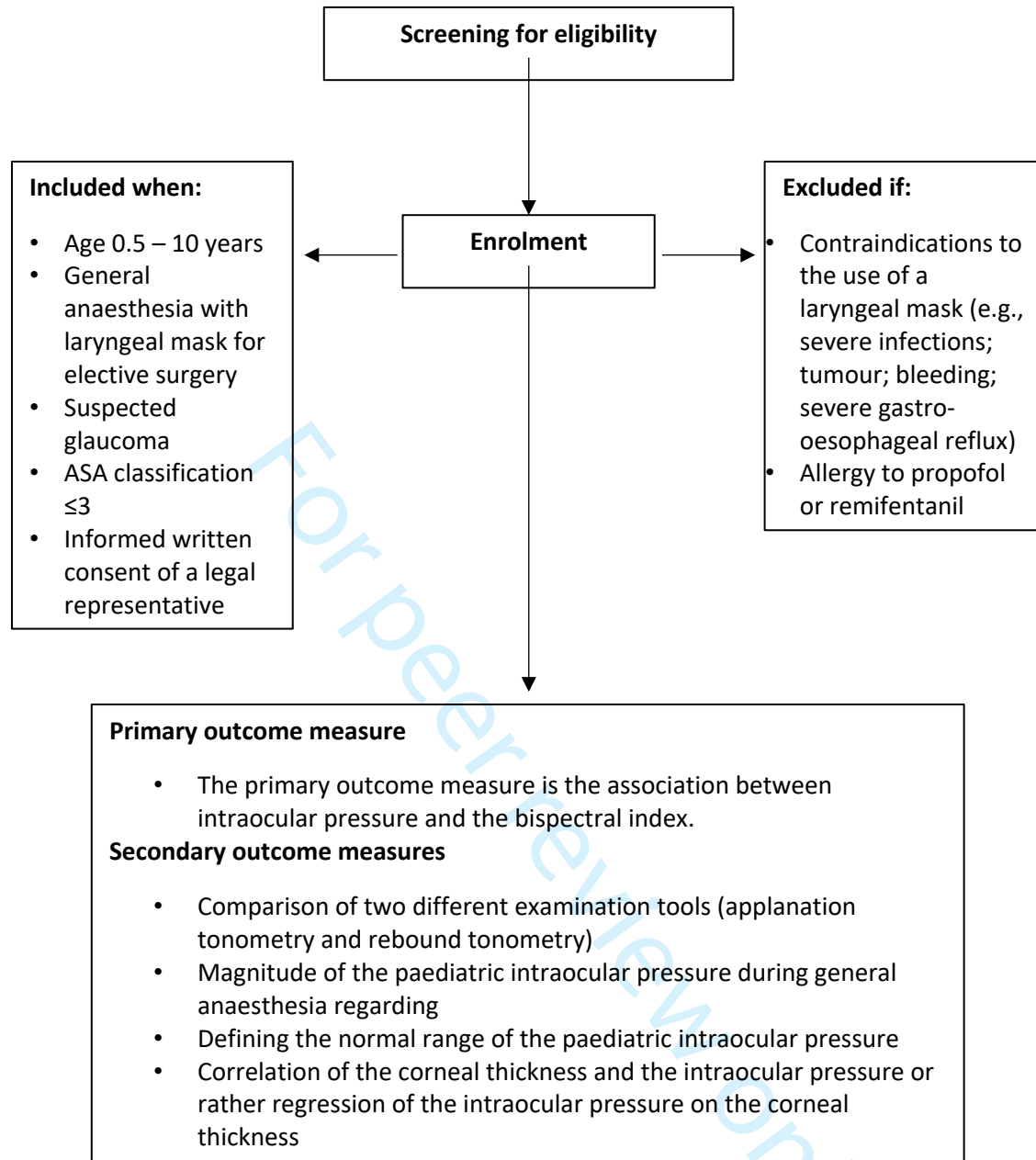
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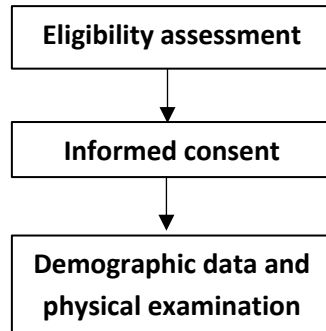
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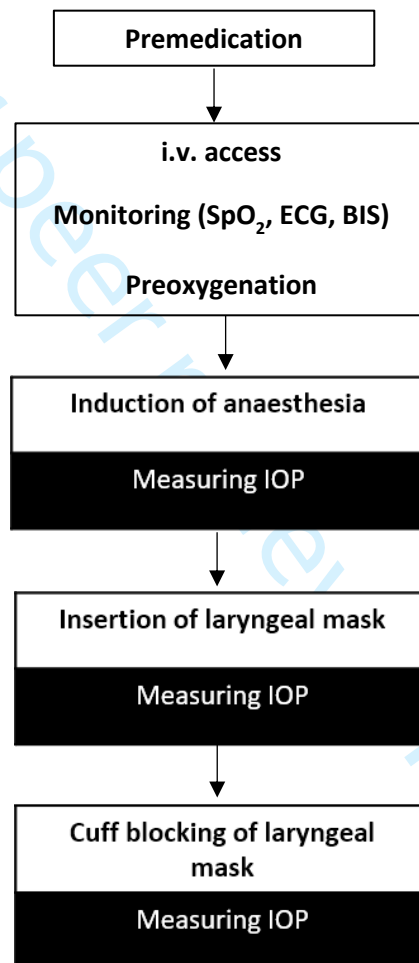
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Day 0



Day 1



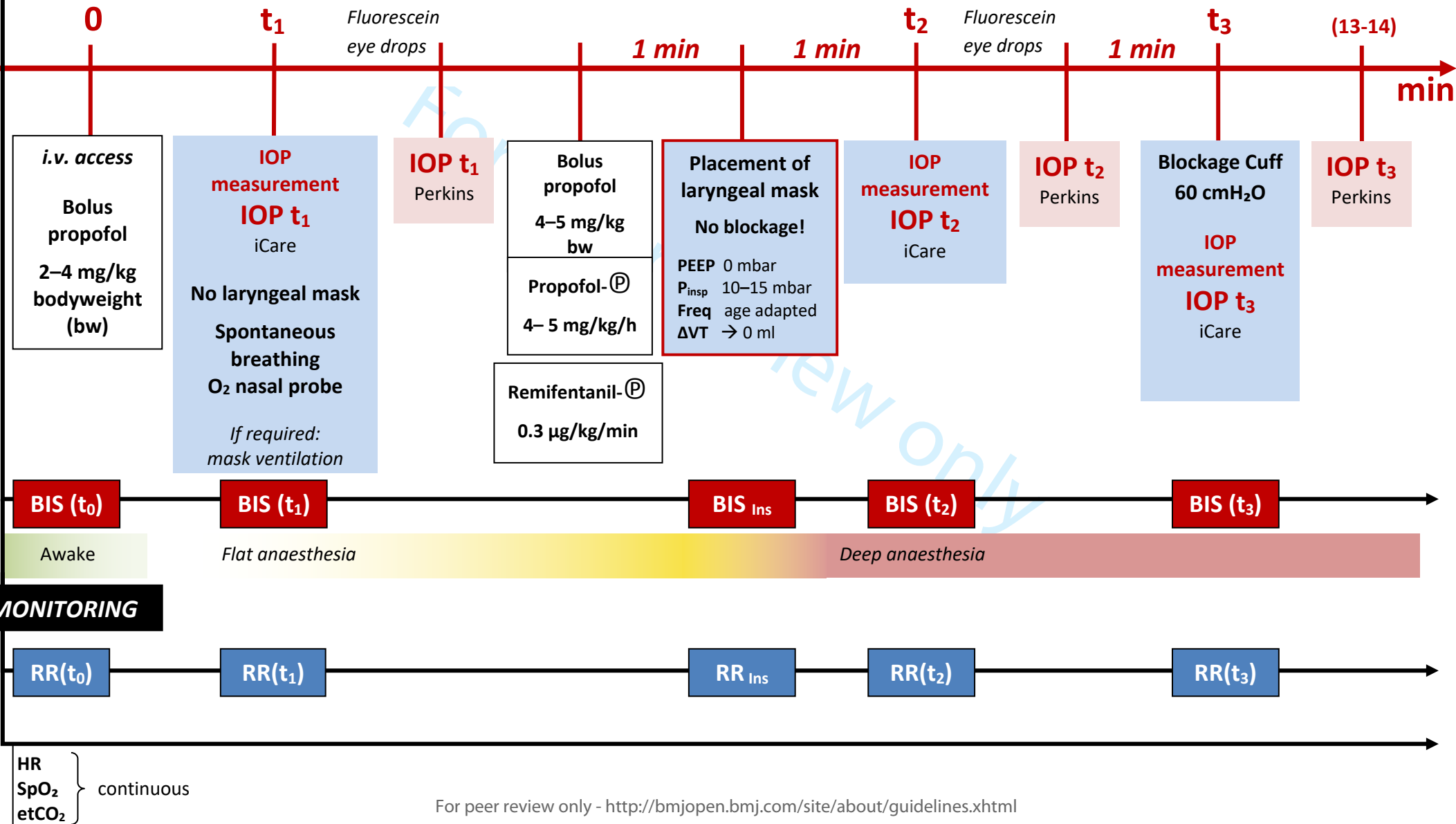


eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

$FiO_2 = 0.8$
Fresh gas flow 7 l/min



Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRIT reporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	n/a
Protocol version	#3	Date and version identifier	n/a
Funding	#4	Sources and types of financial, material, and other support	11
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	11

1	Roles and	#5b	Name and contact information for the trial sponsor	11
2	responsibilities:			
3	sponsor contact			
4	information			
5				
6				
7				
8	Roles and	#5c	Role of study sponsor and funders, if any, in study design;	11
9	responsibilities:		collection, management, analysis, and interpretation of data;	
10	sponsor and funder		writing of the report; and the decision to submit the report for	
11			publication, including whether they will have ultimate	
12			authority over any of these activities	
13				
14				
15				
16	Roles and	#5d	Composition, roles, and responsibilities of the coordinating	11
17	responsibilities:		centre, steering committee, endpoint adjudication committee,	
18	committees		data management team, and other individuals or groups	
19			overseeing the trial, if applicable (see Item 21a for data	
20			monitoring committee)	
21				
22				
23				
24	Introduction			
25				
26				
27	Background and	#6a	Description of research question and justification for	4
28	rationale		undertaking the trial, including summary of relevant studies	
29			(published and unpublished) examining benefits and harms for	
30			each intervention	
31				
32				
33				
34	Background and	#6b	Explanation for choice of comparators	4
35	rationale: choice of			
36	comparators			
37				
38				
39	Objectives	#7	Specific objectives or hypotheses	4
40				
41	Trial design	#8	Description of trial design including type of trial (eg, parallel	5
42			group, crossover, factorial, single group), allocation ratio, and	
43			framework (eg, superiority, equivalence, non-inferiority,	
44			exploratory)	
45				
46				
47				
48	Methods:			
49	Participants,			
50	interventions, and			
51	outcomes			
52				
53				
54				
55	Study setting	#9	Description of study settings (eg, community clinic, academic	5
56			hospital) and list of countries where data will be collected.	
57			Reference to where list of study sites can be obtained	
58				
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1	Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
2				
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6	Interventions:	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
7	description			
8				
9				
10	Interventions:	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	6
11	modifications			
12				
13				
14				
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16				
17	Interventions:	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
18	adherence			
19				
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21				
22	Interventions:	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
23	concomitant care			
24				
25				
26	Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
27				
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37	Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	5
38				
39				
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42				
43	Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9
44				
45				
46				
47				
48	Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
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Methods:

Assignment of interventions (for controlled trials)

1	Allocation: sequence	#16a	Method of generating the allocation sequence (eg, computer-	n/a
2	generation		generated random numbers), and list of any factors for	
3			stratification. To reduce predictability of a random sequence,	
4			details of any planned restriction (eg, blocking) should be	
5			provided in a separate document that is unavailable to those	
6			who enrol participants or assign interventions	
7				
8				
9				
10	Allocation	#16b	Mechanism of implementing the allocation sequence (eg,	n/a
11	concealment		central telephone; sequentially numbered, opaque, sealed	
12	mechanism		envelopes), describing any steps to conceal the sequence until	
13			interventions are assigned	
14				
15				
16				
17	Allocation:	#16c	Who will generate the allocation sequence, who will enrol	5
18	implementation		participants, and who will assign participants to interventions	
19				
20				
21	Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg,	n/a
22			trial participants, care providers, outcome assessors, data	
23			analysts), and how	
24				
25				
26				
27	Blinding (masking):	#17b	If blinded, circumstances under which unblinding is	n/a
28	emergency unblinding		permissible, and procedure for revealing a participant's	
29			allocated intervention during the trial	
30				
31				
32	Methods: Data			
33	collection,			
34	management, and			
35	analysis			
36				
37				
38				
39	Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and	8
40			other trial data, including any related processes to promote	
41			data quality (eg, duplicate measurements, training of	
42			assessors) and a description of study instruments (eg,	
43			questionnaires, laboratory tests) along with their reliability	
44			and validity, if known. Reference to where data collection	
45			forms can be found, if not in the protocol	
46				
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49				
50	Data collection plan:	#18b	Plans to promote participant retention and complete follow-	8
51	retention		up, including list of any outcome data to be collected for	
52			participants who discontinue or deviate from intervention	
53			protocols	
54				
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57	Data management	#19	Plans for data entry, coding, security, and storage, including	8
58			any related processes to promote data quality (eg, double data	
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entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol

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5	Statistics: outcomes	#20a	9
6		Statistical methods for analysing primary and secondary	
7		outcomes. Reference to where other details of the statistical	
8		analysis plan can be found, if not in the protocol	
9			
10	Statistics: additional	#20b	9
11	analyses	Methods for any additional analyses (eg, subgroup and	
12		adjusted analyses)	
13			
14	Statistics: analysis	#20c	9
15	population and	Definition of analysis population relating to protocol non-	
16	missing data	adherence (eg, as randomised analysis), and any statistical	
17		methods to handle missing data (eg, multiple imputation)	
18			
19			
20	Methods: Monitoring		
21			
22	Data monitoring:	#21a	8
23	formal committee	Composition of data monitoring committee (DMC); summary	
24		of its role and reporting structure; statement of whether it is	
25		independent from the sponsor and competing interests; and	
26		reference to where further details about its charter can be	
27		found, if not in the protocol. Alternatively, an explanation of	
28		why a DMC is not needed	
29			
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31			
32	Data monitoring:	#21b	n/a
33	interim analysis	Description of any interim analyses and stopping guidelines,	
34		including who will have access to these interim results and	
35		make the final decision to terminate the trial	
36			
37	Harms	#22	9
38		Plans for collecting, assessing, reporting, and managing	
39		solicited and spontaneously reported adverse events and other	
40		unintended effects of trial interventions or trial conduct	
41			
42			
43	Auditing	#23	9
44		Frequency and procedures for auditing trial conduct, if any,	
45		and whether the process will be independent from	
46		investigators and the sponsor	
47			
48	Ethics and		
49	dissemination		
50			
51			
52	Research ethics	#24	5
53	approval	Plans for seeking research ethics committee / institutional	
54		review board (REC / IRB) approval	
55			
56	Protocol amendments	#25	n/a
57		Plans for communicating important protocol modifications	
58		(eg, changes to eligibility criteria, outcomes, analyses) to	
59			
60			

relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)

1			
2			
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4	Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)
5			
6			
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8			
9	Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable
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14	Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial
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20	Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site
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24	Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators
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29	Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation
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34	Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions
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43	Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers
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47	Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code
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Appendices

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53	Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates
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57	Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the
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1 current trial and for future use in ancillary studies, if
2 applicable
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4 The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND
5 3.0. This checklist was completed on 14. September 2020 using <https://www.goodreports.org/>, a tool made by
6 the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)
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