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

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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

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).

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 EAU 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 administration[4-7]. 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.

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 H_2O); 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 remifentanil. 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

second-generation laryngeal mask with integrated gastric access and the possibility of fibreoptic intubation.[17] Compression of the cervical vessels through the cuff of laryngeal masks has been reported in adults.[18] It has not been investigated whether the blockage of a laryngeal mask in children has an influence on IOP by obstructing the venous return. According to the standard operating procedures of the Department of Anaesthesiology, a premedication with oral midazolam (juice) is administered when the patient is collected from the ward. A dosage of 0.5 mg/kg (up to a maximum dose of 10 mg) is given.

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

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

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

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

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

The schedule of interventions is also summarized in Figure 2.

IOP measurements take place during different depths of anaesthesia. A first IOP measurement is performed when sufficient sedation for IOP measurement after titrated propofol application (2-4 mg/kg or more if necessary) is achieved. A second IOP measurement is carried out 60 s after placement of the laryngeal mask to avoid a potentially falsely high IOP value due to a direct sympathicotonic reaction caused by the laryngeal mask placement. Then, a third IOP measurement is taken after a break of 60 s directly after blockage of the cuff of the laryngeal mask (60 cmH_2O).

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 four 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 mm^2 (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]

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, FiO_2 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

Aim of this 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 in future studies 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 exspiratory CO_2 pressure, blood pressure and heart frequency 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 archived and kept for at least 15 years after completion of the study according to the currently valid ICH Guidelines on Good Clinical Practice (GCP) E6 (R2). Data are accessible to all participating personnel and monitors. The database management system is capable of producing accurate and complete copies of the data in visual form for inspection by government agencies or ethics committees. Enrolled patients and their authorised representative have been informed about this.

Monitoring

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

Adverse events will be recorded after patient enrolment. The study will be temporarily interrupted by the attending investigator at any time on the individual subject, if a serious adverse event is suspected, which may be associated with IOP measurement or an airway device being used. A suspected adverse event or adverse reaction will be considered serious when it comes to one of the following events: death, a life threating reaction leading to inpatient hospitalization, and a persistent or significant incapacity or substantial disability of the normal age-adapted life functions. If the protocol is discontinued as a result of an adverse event, study personnel will document the circumstances and data leading to the discontinuation of measurement. The principal investigator

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

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

Sample size considerations

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

Statistical analysis

For statistical analysis, SAS statistical software will be used. The analysis corresponds to the CONSORT statement for non-pharmacological interventions.

Description of patient group at baseline

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

Analysis of the primary outcome

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

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 CO_2 partial pressure, the blood pressure and the heart rate will also be described by a mixed linear model, with the variables of interest as covariates and random effects for subject and eye and adjustment for corneal thickness.

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 analysed 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 (Sommerset 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 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.

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Author contributions

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

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Declaration of interests

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Provenance and peer review

Not commissioned; externally peer reviewed.

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; SpO_2, 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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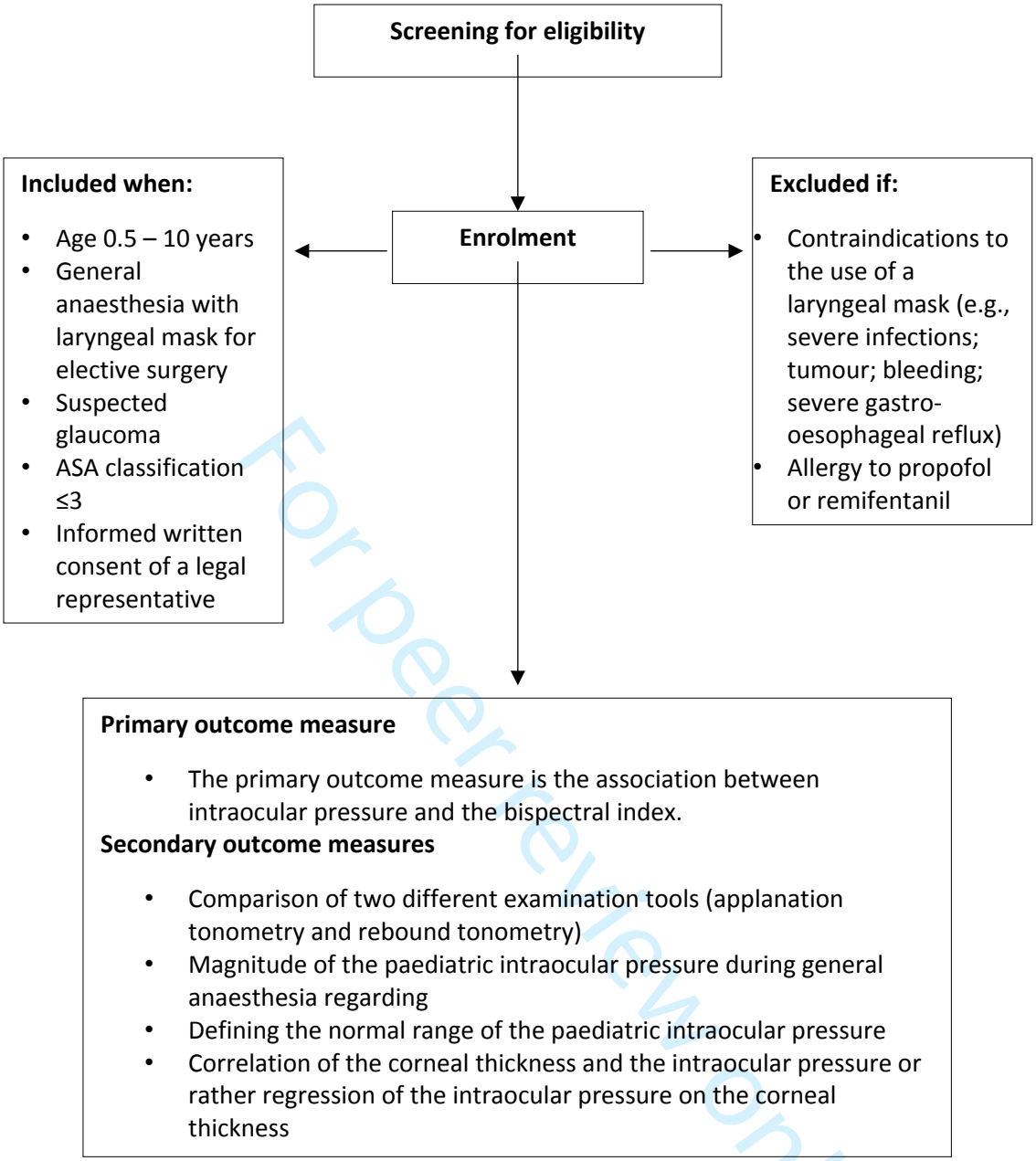

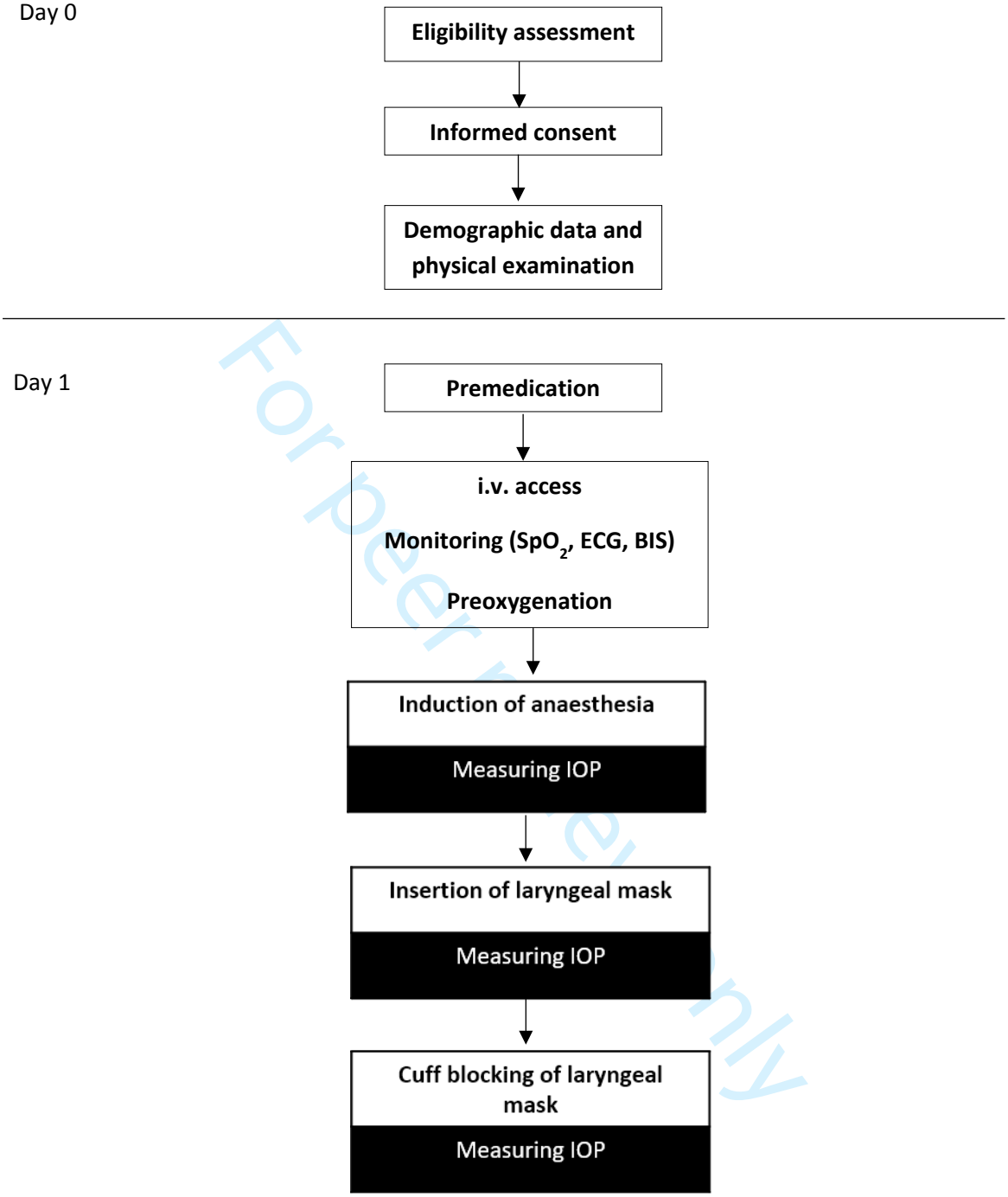

eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

FiO_2 = 0.8

Fresh gas flow 7 l/min

0 | **t_1** | *Fluorescein eye drops* | ***1 min*** | ***1 min*** | **t_2** | *Fluorescein eye drops* | ***1 min*** | **t_3** | **(13-14)** | **min**

i.v. access

Bolus propofol

2–4 mg/kg bodyweight (bw)

IOP measurement

IOP t_1

iCare

No laryngeal mask

Spontaneous breathing

O_2 nasal probe

If required: mask ventilation

IOP t_1

Perkins

Bolus propofol

4–5 mg/kg bw

Propofol-Ⓟ

4– 5 mg/kg/h

Remifentanil-Ⓟ

0.3 µg/kg/min

Placement of laryngeal mask

No blockage!

PEEP 0 mbar
P_{insp} 10–15 mbar
Freq age adapted
ΔVT → 0 ml

IOP measurement

IOP t_2

iCare

IOP t_2

Perkins

Blockage Cuff 60 cmH_2O

IOP measurement

IOP t_3

iCare

IOP t_3

Perkins

BIS (t_0) | **BIS (t_1)** | **BIS $_{Ins}$** | **BIS (t_2)** | **BIS (t_3)**

Awake | *Flat anaesthesia* | *Deep anaesthesia*

MONITORING

RR(t_0) | **RR(t_1)** | **RR $_{Ins}$** | **RR(t_2)** | **RR(t_3)**

HR
SpO_2
$etCO_2$
} continuous

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 SPIRITreporting 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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#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

		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

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	n/a
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	8
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	n/a
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	n/a
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	n/a
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	n/a

BMJ Open

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

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

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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-Kommisssion der Landesaerztekammer 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.

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 EAU 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 administration[4-7]. 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 H_2O); 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 remifentanil. 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

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 (Ethik-Kommission der Landesaerztekammer Rheinland-Pfalz), 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 second-generation laryngeal mask with integrated gastric access and the possibility of fibreoptic intubation.[17] Compression of the cervical vessels through the cuff of laryngeal masks has been reported in adults.[18] It has not been investigated whether the blockage of a laryngeal mask in children has an influence on IOP by obstructing the venous return. According to the standard operating procedures of the Department of Anaesthesiology, a premedication with oral midazolam (juice) is administered when the patient is collected from the ward. A dosage of 0.5 mg/kg (up to a maximum dose of 10 mg) is given.

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

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

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

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

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

The schedule of interventions is also summarized in Figure 2.

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

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 mm^2 (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, FiO_2 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 CO_2 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

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

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

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

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

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

For statistical analysis, SAS statistical software will be used. The analysis corresponds to STROBE statement for observational studies.

Description of patient group at baseline

The baseline features of patients will be described using absolute numbers (n) and percentages for categorical variables and the minimum, maximum, mean and standard deviation for normally distributed variable and as median (IQR) for non-Gaussian variables. The Pearson correlation coefficient will be used to compare patient specifics between the 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 CO_2 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 (Sommerset 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

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.

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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.

Open Access

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; SpO_2, 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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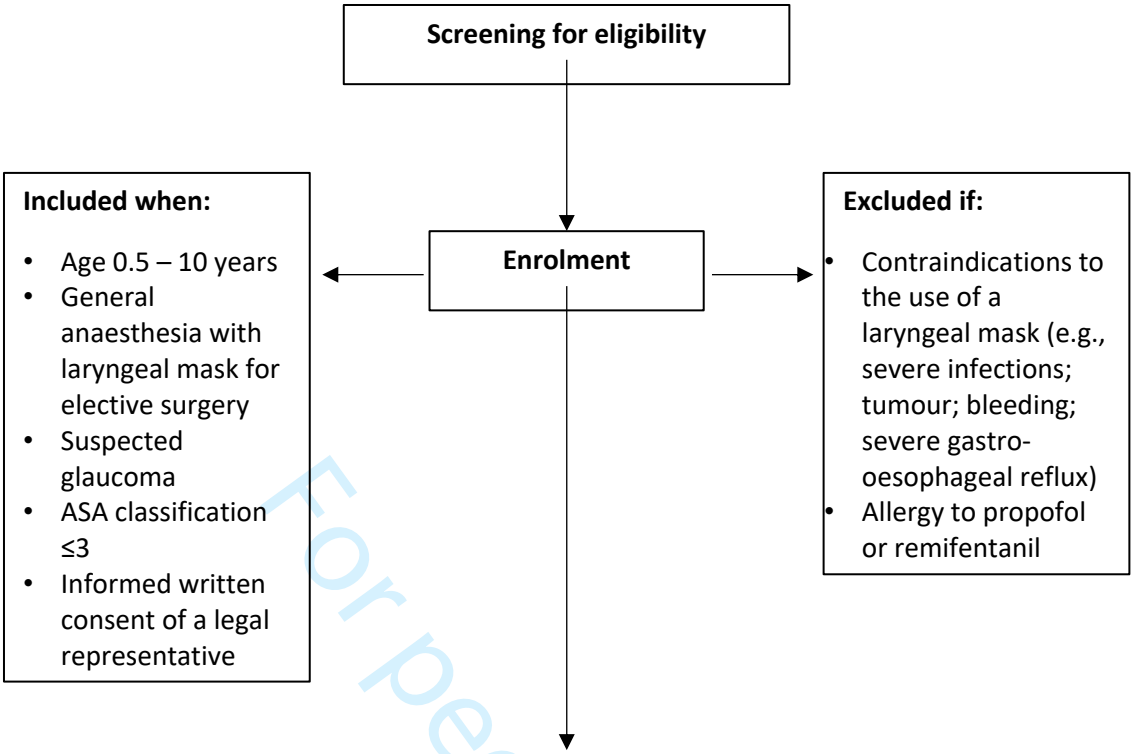
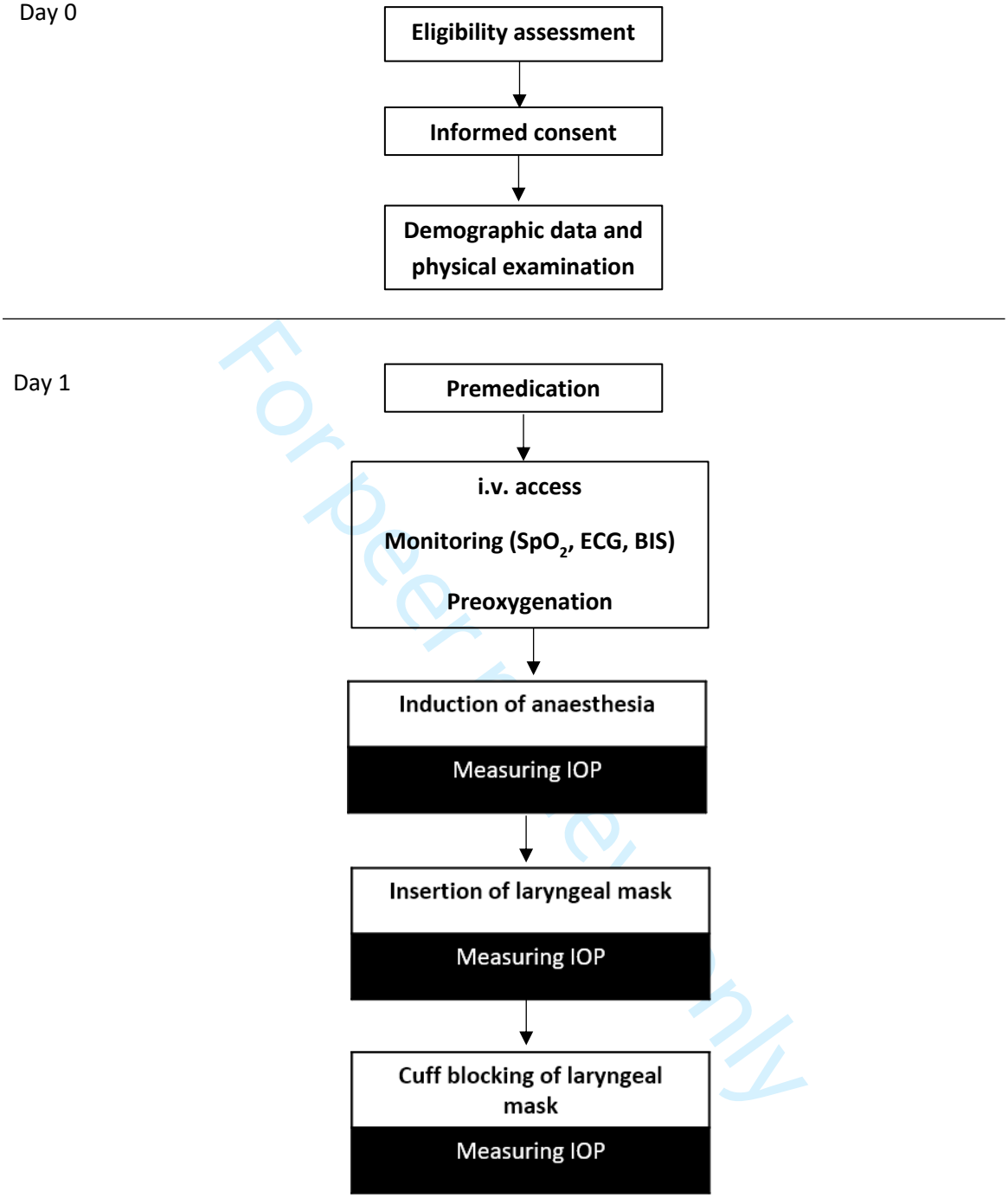


Primary outcome measure

- The primary outcome measure is the association between intraocular pressure and the bispectral index.

Secondary outcome measures

- Comparison of two different examination tools (applanation tonometry and rebound tonometry)
- Magnitude of the paediatric intraocular pressure during general anaesthesia regarding
- Defining the normal range of the paediatric intraocular pressure
- Correlation of the corneal thickness and the intraocular pressure or rather regression of the intraocular pressure on the corneal thickness



eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

FiO_2 = 0.8

Fresh gas flow 7 l/min

0 | **t_1** | *Fluorescein eye drops* | **1 min** | **1 min** | **t_2** | *Fluorescein eye drops* | **1 min** | **t_3** | **(13-14)** | **min**

i.v. access

Bolus propofol

2–4 mg/kg bodyweight (bw)

IOP measurement

IOP t_1

iCare

No laryngeal mask

Spontaneous breathing

O_2 nasal probe

If required: mask ventilation

IOP t_1

Perkins

Bolus propofol

4–5 mg/kg bw

Propofol-Ⓟ

4– 5 mg/kg/h

Remifentanil-Ⓟ

0.3 µg/kg/min

Placement of laryngeal mask

No blockage!

PEEP 0 mbar
P_{insp} 10–15 mbar
Freq age adapted
ΔVT → 0 ml

IOP measurement

IOP t_2

iCare

IOP t_2

Perkins

Blockage Cuff 60 cmH_2O

IOP measurement

IOP t_3

iCare

IOP t_3

Perkins

BIS (t_0) | **BIS (t_1)** | **BIS $_{Ins}$** | **BIS (t_2)** | **BIS (t_3)**

Awake — *Flat anaesthesia* — *Deep anaesthesia*

MONITORING

RR(t_0) | **RR(t_1)** | **RR $_{Ins}$** | **RR(t_2)** | **RR(t_3)**

HR
SpO_2
$etCO_2$
} continuous

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 SPIRITreporting 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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#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
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	8

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	n/a

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	8
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	n/a
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	n/a
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Additional attachment
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the	n/a

current trial and for future use in ancillary studies, if applicable

BMJ Open

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

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Keywords:	Anaesthesia in ophthalmology < ANAESTHETICS, Paediatric anaesthesia < ANAESTHETICS, Glaucoma < OPHTHALMOLOGY, Paediatric ophthalmology < OPHTHALMOLOGY

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

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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-Kommisssion der Landesaerztekammer 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.

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 EAU 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 administration[4-7]. 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 H_2O); 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 remifentanil. 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

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 (Ethik-Kommission der Landesaerztekammer Rheinland-Pfalz), 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 second-generation laryngeal mask with integrated gastric access and the possibility of fibreoptic intubation.[17] Compression of the cervical vessels through the cuff of laryngeal masks has been reported in adults.[18] It has not been investigated whether the blockage of a laryngeal mask in children has an influence on IOP by obstructing the venous return. According to the standard operating procedures of the Department of Anaesthesiology, a premedication with oral midazolam (juice) is administered when the patient is collected from the ward. A dosage of 0.5 mg/kg (up to a maximum dose of 10 mg) is given.

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

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

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

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

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

The schedule of interventions is also summarized in Figure 2.

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

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 mm^2 (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, FiO_2 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 CO_2 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

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

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

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

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

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

For statistical analysis, SAS statistical software will be used. The analysis corresponds to STROBE statement for observational studies.

Description of patient group at baseline

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

The Pearson correlation coefficient will be used to compare patient specifics between the 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 CO_2 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 (Sommerset 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 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.

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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

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Provenance and peer review

Not commissioned; externally peer reviewed.

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; SpO_2, 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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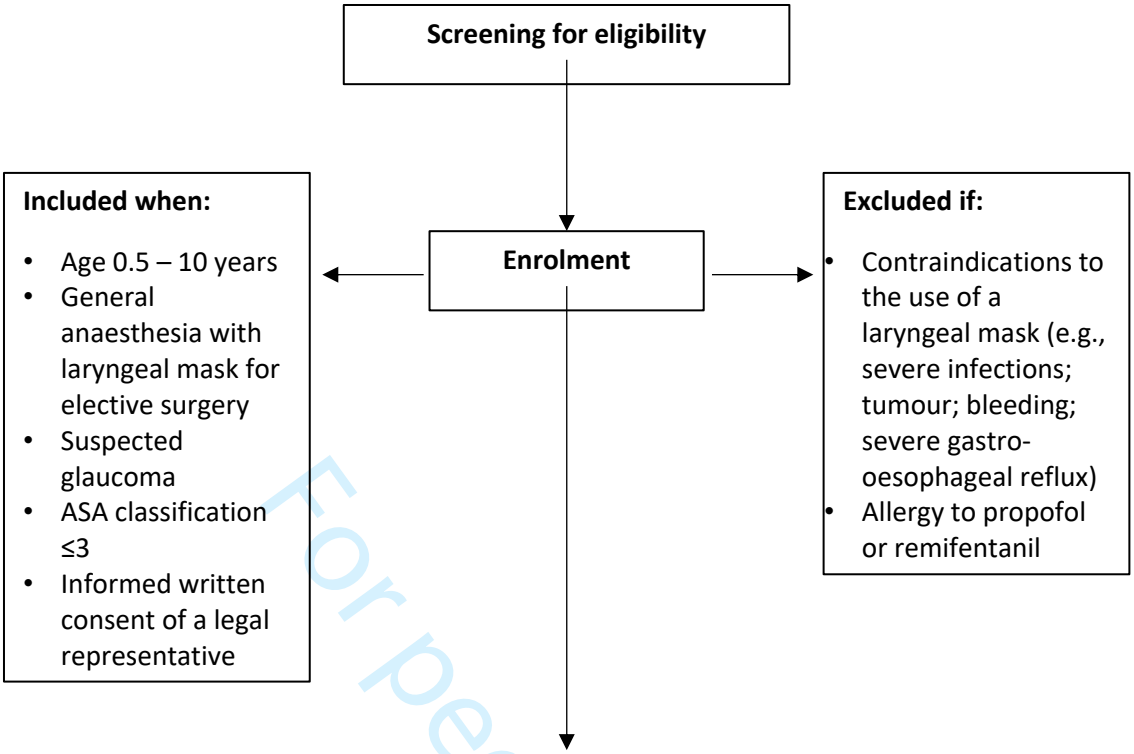
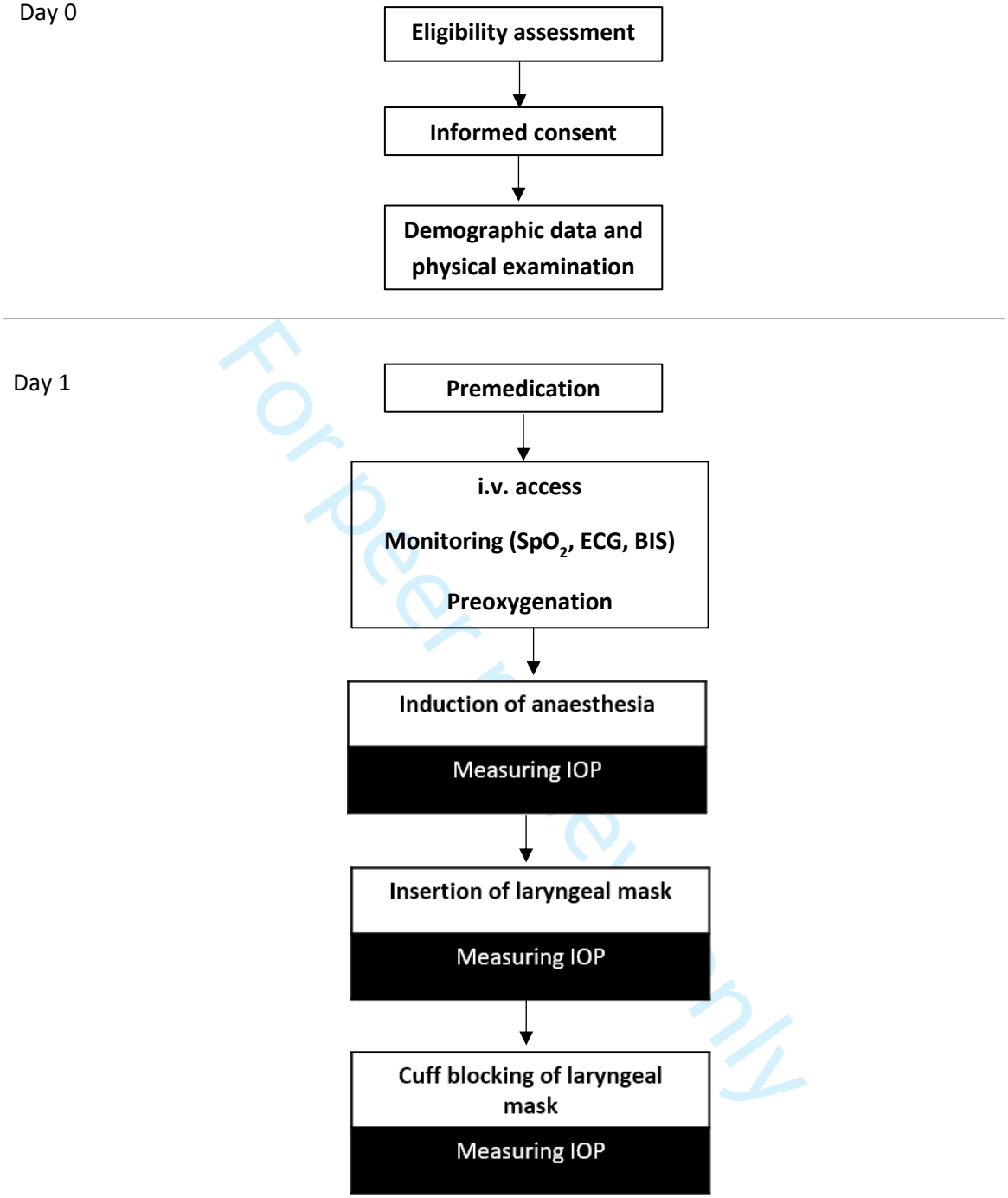


Primary outcome measure

- The primary outcome measure is the association between intraocular pressure and the bispectral index.

Secondary outcome measures

- Comparison of two different examination tools (applanation tonometry and rebound tonometry)
- Magnitude of the paediatric intraocular pressure during general anaesthesia regarding
- Defining the normal range of the paediatric intraocular pressure
- Correlation of the corneal thickness and the intraocular pressure or rather regression of the intraocular pressure on the corneal thickness



eyeBIS Worksheet Anaesthesia

TIVA

Preoxygenation

FiO_2 = 0.8

Fresh gas flow 7 l/min

0 | **t_1** | *Fluorescein eye drops* | **1 min** | **1 min** | **t_2** | *Fluorescein eye drops* | **1 min** | **t_3** | **(13-14)** | **min**

i.v. access

Bolus propofol

2–4 mg/kg bodyweight (bw)

IOP measurement

IOP t_1

iCare

No laryngeal mask

Spontaneous breathing

O_2 nasal probe

If required: mask ventilation

IOP t_1

Perkins

Bolus propofol

4–5 mg/kg bw

Propofol-Ⓟ

4– 5 mg/kg/h

Remifentanil-Ⓟ

0.3 µg/kg/min

Placement of laryngeal mask

No blockage!

PEEP 0 mbar
P_{insp} 10–15 mbar
Freq age adapted
ΔVT → 0 ml

IOP measurement

IOP t_2

iCare

IOP t_2

Perkins

Blockage Cuff 60 cmH_2O

IOP measurement

IOP t_3

iCare

IOP t_3

Perkins

BIS (t_0) | **BIS (t_1)** | **BIS $_{Ins}$** | **BIS (t_2)** | **BIS (t_3)**

Awake — *Flat anaesthesia* — *Deep anaesthesia*

MONITORING

RR(t_0) | **RR(t_1)** | **RR $_{Ins}$** | **RR(t_2)** | **RR(t_3)**

HR
SpO_2
$etCO_2$
} continuous

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 SPIRITreporting 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

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	11
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	11
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5

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
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6
Interventions: modifications	#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
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	6
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	6
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
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
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
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	5
Methods: Assignment of interventions (for controlled trials)			

Allocation: sequence generation	#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
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	8

		entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
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
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	9
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	9
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	8
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	n/a
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	9
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	9
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	5
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to	n/a

		relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	10
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	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	11
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	8
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	n/a
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	n/a
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	11
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	n/a
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	Additional attachment
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the	n/a

current trial and for future use in ancillary studies, if applicable