Smartphone virtual reality exposure before paediatric surgery: effects on pre- and post-procedural pain and anxiety.
A multicentre study

Smartphone virtual reality exposure before surgery: effects on pre- and post-procedural pain and anxiety (PREVIEW 2).

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AVG	Algemene Verordening Gegevensbescherming
CAU	Care as usual
CBCL	Child Behavior Checklist
CEA	continuous epidural administration
CRF	Case Report Form
FPS	Faces Pain Scale
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
mYPAS	Modified Yale Preoperative Anxiety Scale
NRS	Numeric Rating Scale
PCEA	patient-controlled epidural analgesia
PIF	Patient Information Form
PROMIS	Patient Reported Outcomes Measurement Information System
RCT	Randomized controlled trial
(S)AE	(Serious) Adverse Event
SDV	Source Document Verification
SES	Socio-economic State
STAI	State-Trait Anxiety Inventory
SUSAR	Suspected Unexpected Serious Adverse Reaction
sVRE	Smartphone Virtual Reality Exposure
VR	Virtual Reality
VRE	Virtual Reality Exposure
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: Fifty percent of children and 80% of adolescents experience anxiety and distress prior to surgery. Preoperative anxiety is related to higher levels of post-operative pain and sleep problems. We recently showed that half as many children that received preoperative Virtual Reality Exposure (VRE) prior to anaesthesia for tonsillectomy needed morphine compared to children who did not receive this preparation. However, there are some disadvantages to this VRE, e.g. it is installed on a PC at the Sophia Children's Hospital, which limits the implementation of this intervention. Therefore, we further developed this VRE into a smartphone app with the aim of improved exposure to the VRE (at home, at a child's own pace) and reducing healthcare costs.

This study aims to test the efficacy of this smartphone VRE application (sVRE) versus care as usual (CAU) in children undergoing major and/or painful surgery on postoperative pain and analgesics use. Our hypotheses are: (1) sVRE will be significantly more efficacious than care as usual (CAU) on both primary (postoperative pain) and secondary outcomes, and (2) children with unfavourable predictor variables will benefit more from sVRE.

Objective: The objectives of this study are to (1) test the efficacy of sVRE versus CAU in 180 children undergoing surgery on the postoperative pain of the child (primary outcome), postoperative analgesics use, anxiety level of the child during induction of anaesthesia, compliance during induction of anaesthesia, postoperative sleep problems, and length of hospital stay (secondary outcomes). (2) To examine predictors of VRE efficacy, including socioeconomic status (SES), age, sex, number of prior surgeries, preoperative child and parental anxiety, and preoperative sleep problems. These analyses were be performed for children with scoliosis surgery and (A)TE separately.

Study design: A multicentre, randomized controlled trial (RCT) in which 180 participants (128 patients undergoing (adeno)tonsillectomy ((A)TE) and 52 patients undergoing scoliosis surgery) will be allocated to either the sVRE intervention condition (n=90) or CAU (n=90). The longitudinal design will include six measurements points: Pre-intervention, two weeks before surgery (T0); post-intervention, prior to entering surgery room (T1); during induction of anaesthesia (T2); postoperatively in the recovery room (T3); 5 days postoperative (T4); and 21 days postoperative (T5; only for scoliosis surgery). The two groups (i.e., scoliosis surgery and (A)TE) will be examined separately.

Study population: Eligible are all consecutive paediatric patients (aged 6 up to 18 years), undergoing scoliosis surgery at the Sophia Children's Hospital or (A)TE at Maasstad Hospital, between January 2023 and December 2023.

Intervention: sVRE preparation encompasses a virtual, three-dimensional environment that replicates the operating rooms of the Sophia Children's Hospital. This virtual 3D environment contains the waiting room, corridor to the operating room, operating room and recovery room. The procedures children will undergo before they are induced for anaesthesia are also animated in the sVRE environment. Children can use the VR preparation at home with a smartphone VR app and plastic VR glasses. The smartphone app provides the child the opportunity to fully look around in the virtual 3D environment and thus explore the sVRE environment at his own pace, in a child-friendly way, as often as the child wants.

Main study parameters/endpoints: The main study parameter is postoperative pain upon awakening from anaesthesia (T3) assessed with the observational, Face, Legs, Activity, Cry, Consolability (FLACC) scale and a Faces Pain Scale (FPS) from 0 (no pain) to 10 (worst imaginable pain) .

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The risks are negligible and the burden is minimal. All children receive care as usual, and those who are randomized to the sVRE condition will wear plastic VR glasses to use the sVRE application. Since this VRE is performed at home, there is a risk that children run into tables, chairs or other furniture. To limit this risk, parents and children are instructed to only use the sVRE intervention when an adult/guardian is present. Moreover, it cannot be ruled out that some children will become stressed and anxious during the VR. If this is the case, parents are instructed to immediately terminate the sVRE procedure and comfort the child. If there is a need for acute psychosocial care, adequate referral will be arranged. If children will be allocated to the CAU group, no risks are incurred beyond those associated with CAU.

The only potential burden for parents and children are the short assessments. The burden for children is minimal, as they only rate their pain on a FPS and anxiety on a Numeric Rating Scale (NRS) and complete questionnaires on the user experience and sleep (if aged 8 years or older). The burden for parents is also minimal, as they only complete a number of questionnaires.

1. INTRODUCTION AND RATIONALE

Introduction. Thousands of children undergo surgery in the Sophia Children's Hospital and Maasstad hospital every year. Fifty to 80% of children and adolescents, respectively, experience anxiety and distress prior to surgery[1, 2]. This anxiety has negative influence on the induction of anaesthesia, e.g. these children are more often agitated, cry more and cooperate less than non-anxious children[3]. Moreover, preoperative anxiety is related to higher levels of post-operative pain, emergence delirium and sleep problems[4, 5], which slows down recovery and increases the use of pain medication (analgesics).

Throughout the years, several interventions have been introduced to reduce preoperative anxiety, for example the use of midazolam and the presence of a parent during anaesthesia induction[6]. Although effective at reducing preoperative anxiety, these interventions also have disadvantages. For example, midazolam has adverse side effects and the anxiety level of a parent may negatively influence the anxiety of the child. Therefore, it is important to further develop interventions that reduce preoperative anxiety and postoperative pain in children.

A recent meta-analysis[7] suggested that distraction via Virtual Reality (VR) is an effective intervention to reduce anxiety and pain during medical procedures. However, distraction techniques are not always possible and are time consuming. Exposure on the other hand, is a technique whereby children are gradually exposed to dreaded situations. Exposure is generally a more effective way to reduce anxiety with more lasting results[8]. The same analysis showed that research on the use of VR as exposure prior to surgery is scarce.

Previous data. Two studies by Ryu et al.[9, 10] showed that VR leads to reduced pre-operative anxiety. However, they did not include post-operative assessments of anxiety, pain or sleep problems. Eijlers et al.[11] were the first to include post-operative assessments of anxiety and pain in a randomized controlled trial that investigated the effectiveness of a VR exposure program (n = 200). This VR program showed all operating environments (waiting room, corridor, operating room and recovery room) realistically. Also, all the procedures that children experience before and after an operation were shown. Participants received VR exposure on the day of the surgery in the hospital due to dependency on hardware located in the hospital. The results showed that in the children who underwent the most painful operation (tonsillectomy), half as many children who received the VR preparation needed morphine directly postoperatively compared to children who did not receive this preparation.

Clinical importance. The result by Eijlers et al.[11] has significant clinical importance given the side effects of morphine and other analgesics and the risk of dependence that the use of opiates (morphine) entails. Also, although pain scores were low to moderate in this study, the morphine need shows that these children experienced more pain and discomfort postoperatively. It is known that if acute (postoperative) pain is not treated adequately, these is an increased risk of the pain to become chronic[12, 13]. Especially orthopaedic operations, e.g. scoliosis surgery, are painful operations with a significant risk of developing chronic post-surgical pain. Chronic pain is a major problem for society as chronic pain during adolescence has a high economic impact and is associated with an increased risk of having chronic pain as an adult[14].

Limitations and innovative aspects of smartphone VR exposure. The positive results for VR exposure on pain medication show that it is beneficial to implement VR exposure in the preparation procedure for paediatric surgery. However, there are some limitations. First, the VR programme was installed on a PC at the hospital. VR exposure via a smartphone application will have several advantages, such as cost-effectiveness and easy accessibility. Moreover, it offers the possibility for children and their parents to get familiarized with the hospital environment in a child-friendly, fancy, realistic, interactive, and innovative manner in children's own home environment. Moreover, the VR smartphone app allows children to experience the surgery environment and procedures as often as needed.

Second, no effects were found on anxiety at induction of anaesthesia and post-operative pain, which might be explained due to the inclusion of patients who underwent small procedures in day care only in an academic hospital setting with great emphasise on patient comfort. Further investigation of VR exposure in more painful or major procedures and including general hospitals is necessary to increase generalizability of the previous results. The development of a generic smartphone VR exposure app makes this more convenient as it will be easier to implement VR exposure in standard care.

Third, despite the associations of preoperative anxiety with sleep problems[4] and sleep problems with post-operative pain[15], sleep was not included as an outcome measurement. The inclusion of this secondary measurement might provide more insight in the working mechanism of the positive effect of VR exposure on pain.

Conclusion. Smartphone VR is a promising and easy accessible way to prepare thousands of children on painful or major surgery in their home environment before the actual surgery. Such a mobile VR preparation tool has important advantages for patient well-being (less anxiety and pain) and cost-effectiveness (less analgesics and side effects and shorter hospital stay).

Overall aim. This RCT primarily aims to test the efficacy of a smartphone VR exposure (sVRE) application versus care as usual (CAU) in children undergoing major and/or painful surgery on postoperative pain, use of pain medication, pre- and postoperative child anxiety, pre- and postoperative sleep problems, health care use, and pre- postoperative parental anxiety, both in a specialized children's hospital and a large general hospital. The second aim is to examine predictors of sVRE efficacy. Predictor variables that will be examined are socioeconomic status (SES), age, sex, type of surgery, number of prior surgeries, child and parental anxiety, and child psychopathology in the previous six months.

Hypothesis. We hypothesize that

(1) sVRE will be significantly more efficacious than CAU on both primary and secondary outcomes, and

(2) children with unfavourable predictor variables will benefit more from sVRE.

2. OBJECTIVES

Primary Objective

The primary objective is to examine the efficacy of sVRE versus CAU in 128 children, aged 6 up to 18 years, undergoing (adeno)tonsillectomy surgery and 52 children, aged 8 up to 18 years, undergoing scoliosis, on:

a) The primary outcome: postoperative pain upon awakening after anaesthesia.
b) The secondary outcomes:
    - Postoperative analgesics use
    - Anxiety level of the child during induction of anaesthesia
    - Compliance during induction of anaesthesia
    - Pre- and postoperative child anxiety
    - User experience
    - Post-operative sleep problems
    - Length of hospital stay

Secondary Objective

The secondary objective is to identify which variables predict the efficacy of sVRE. Predictor variables that will be examined are:

- SES
- Age
- Sex
- Type of surgery
- Number of prior surgeries
- Preoperative child anxiety
- Preoperative parental anxiety
- Sleep problems prior to surgery

3. STUDY DESIGN

A multicentre, single-blinded RCT will be carried out in the Erasmus MC-Sophia and the Maasstad Hospital. This RCT involves a psychosocial intervention (sVRE) versus CAU in children who will undergo (adeno)tonsillectomy (N=128; Maasstad Hospital) or scoliosis surgery (N=52; Erasmus MC-Sophia). More information on the sVRE intervention is provided in section 5.1.

The duration of the study is approximately 2 weeks for participants who will undergo (A)TE and approximately 4 weeks for participants who will undergo scoliosis surgery. This duration includes 1 week of the sVRE intervention or CAU and five measurement points. Figure 1 gives an overview of the study design and the questionnaires that need to be completed at each measurement point. More information about the questionnaires is provided in section 8.

Figure 1: **Flow chart of study design**

Informed consent			
T0: Pre-intervention, online assessment at home	• Pain child	FPS	(child)
	• Anxiety child	NRS	(child)
	• Anxiety parent	STAI	(parent)
	• Sleep child	PROMIS	(parent/child)[a]
	• Sociodemographics		(parent)
Randomization (sVRE or CAU)			
			
T1: Post intervention, assessment prior to going to the operating room	• Pain child	FPS	(child)
	• Anxiety child	NRS	(child)
	• User experience app	self-developed questionnaire	
T2: Induction of anesthesia	• Anxiety child	mYPAS	(psychologist)
	• Compliance child	ICC	(psychologist)
T3: Recovery room[b]	• Pain child	FPS	(child)
		FLACC	(psychologist)
	• Anxiety child	NRS	(child)
	• Analgesic use	patient dossier	
T4: 5 days after the operation	• Pain child	FPS	(child)
	• Anxiety child	NRS	(child)
	• Sleep child	PROMIS	(parent/child)[a]
	• Analgesics use	parents[c]	
T5: 21 days after the operation[c]	• Analgesics use	parents[c]	

FLACC = Face, Legs, Activity, Cry, Consolability scale; FPS = Faces Pain Scale; ICC = Induction Compliance Checklist; mYPAS = modified Yale Preoperative Anxiety Scale; NRS = Numeric Rating scale; PROMIS = PROMIS sleep disturbance; STAI = State-Trait Anxiety Inventory.

[a] For children aged 6 and 7 years old, parents will complete a parent proxy of the PROMIS Sleep Disturbance scale. Children aged 8 years and older will complete a children's version of the PROMIS Sleep Disturbance scale.

[b] The FPS, NRS and FLACC are assessed at several moments in the recovery room starting upon awakening and repeated every 10 minutes until discharge. For the scoliosis patients, the NRS will also be assessed during hospitalization, three times a day.

[c] For ATE patients, analgesics use will be collected at 5 days after the operation. There will be no measurement at 21 days after surgery. For scoliose patients, analgesics use during hospitalization will be derived from medical records. Analgesics use after discharge will be collected 21 days after the operation.

4. STUDY POPULATION

4.1 Population (base)

(adeno)tonsillectomy

The target group of this study consists of children aged 6 up to 18 years undergoing a (A)TE at the Maasstad Hospital between January 2023 and December 2023. On an annual basis, about 500 tonsillectomies are done at Maasstad Hospital. Considering our previous studies with children and the popularity of VR, we expect a participation rate of >80%. Twelve months of data gathering will be sufficient to recruit the necessary 128 participants (see section 4.4), who will be randomly assigned to the sVRE group (n=64) or the CAU group (n=64). Data collection will stop when 128 participants completed all measurements.

Scoliosis

The target group of this study consists of children aged 8 up to 18 years undergoing scoliosis surgery at the Erasmus MC-Sophia between January 2023 and December 2023. On an annual basis, about 80 scoliosis operations are performed at the Erasmus MC-Sophia. A previous study in this population assessing pain measurements recruited 45 participants in a similar time period (October 2016 until December 2017). Considering our previous studies with children and the popularity of VR, we expect recruitment to be easier for this trial. Based on these numbers, we think it is realistically feasible to include 52 participants (see section 4.4), who will be randomly assigned to the sVRE group (n=26) or the CAU group (n=26).

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- (A)TE: 6 up to 18 years old at baseline.
- Scoliosis: 8 up to 18 years old at baseline.
- Undergoing surgery for scoliosis (either idiopathic scoliosis or non-idiopathic scoliosis patients receiving an open dorsal spinal fusion) or (adeno)tonsillectomy between January 2023 and December 2023.

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Mental retardation
- Severe visual disability
- Preoperative use of anxiolytic medication.
- In case of non-idiopathic scoliosis: loss of sensation, for example caused by spina bifida or paraplegia.
- Inability to read and write Dutch

4.4 Sample size calculation

(Adeno)tonsillectomy

A sample size of 128 (n=64 per group) is sufficient to detect a medium effect size (Cohen's f = 0.25) with a power of 80% and an alpha of 0.05 with a ANOVA. In addition, we can perform repeated measures ANOVA's for four time points with a power of 0.96 (Cohen's f = 0.25, α = .05). N=64 in the intervention group is sufficient to perform regression analyses using 2 predictor variables (80% power, small to medium effect size).

Scoliosis

A sample size of 52 (n = 26 per group) is sufficient to detect a large effect size (Cohen's f = 0.40) with a power of 80% and an alpha of 0.05 with a ANOVA. In addition, we can perform repeated measures ANOVA's for four time points with a power of 0.81 (Cohen's f = 0.30, α = .05).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

sVRE preparation encompasses a virtual, three-dimensional environment that replicates the operating rooms of the Sophia Children's Hospital and the Maasstad Hospital. This virtual 3D environment contains the waiting room, corridor to the operating room, operating room and recovery room. The procedures children will undergo before they are induced for anaesthesia are also animated in the sVRE environment (i.e. application of intravenous line, blood pressure cuff, pulse oxi meter, and placement of ECG stickers). Children can use the VR preparation at home with a smartphone VR app and plastic VR glasses. The smartphone app provides the child the opportunity to fully look around in the virtual 3D environment and thus explore the sVRE environment at his own pace, in a child-friendly way, as often as the child wants. In this way the child becomes acquainted in an interactive way with the hospital environment and procedures that it will undergo.

CAU for the Sophia Children's Hospital means that children and their parents are advised by their anaesthesiologist or attending physician to watch the informative online movie of the Erasmus MC-Sophia (www.erasmusmc.nl/anesthesiefilmsophia). There are different versions of the movie available for children of 4-7 years old and of 8-12 years old, with a duration of approximately 15 minutes. For the Maasstad Hospital, CAU means that children and their parents are advised by their anaesthesiologist or attending physician to watch the informative online movie (https://www.youtube.com/watch?v=P7lgzK24h-E). In addition, a childcare worker is present in the preparation room to assist the child.

Standard anaesthesia and pain medication

As postoperative pain is the primary outcome, all children included in the investigation will receive a standardized anaesthesia regimen. Children will not receive any oral or intravenous anxiolytic premedication, such as clonidine or midazolam, preoperatively. All analgesic use during the procedure, on the recovery ward, on the day care unit, and at home (until three days postoperatively) will be recorded.

(Adeno)tonsillectomy

General anaesthesia is induced by a mask induction with sevoflurane in a mixture of oxygen and air or by intravenous administration of propofol (2-4 mg/kg). Intravenous access will be established when the child is deeply sedated. The child receives an endotracheal tube, and anaesthesia is maintained with sevoflurane in oxygen/air mixture. Also, during (adeno)tonsillectomy, the child receives dexamethasone (0,15mg/kg). The child receives a

first dose of paracetamol (20 mg/kg) and diclofenac (1 mg/kg) as suppository preoperatively.

After the surgical procedure, the child is admitted to the recovery ward. If the child has a pain score of > 4 on the numerical rating scale, morphine may be titrated intravenously (0.1 mg/kg) on the recovery ward. The child receives paracetamol (90 mg/kg/day orally or rectally) and diclofenac (3 mg/kg/day orally or rectally) as postoperative pain medication for four days.

Scoliosis

Adolescents undergoing scoliosis surgery included in this study are not allowed to have anxiolytic premedication such as midazolam before they come to the OR. General anaesthesia is induced by intravenous administration of propofol (3-4 mg/kg) and sufentanil (0.3 microgram/kg). If intravenous access is difficult, the child will receive a mask induction with sevoflurane in a mixture of oxygen and air. When the child is deeply sedated, intravenous access will be established. The child receives an endotracheal tube, and anaesthesia is maintained with propofol (6-10 mg/kg/h) and sufentanil (0.2-0.4 mcg/kg/h) continuous intravenously, sometimes combined with remifentanil (0.1-0.5 mcg/kg/h IV). . Before endotracheal tube placement, the child receives a muscle relaxant (rocuronium).

Postoperative pain management includes a cranial continuous epidural administration of a mixture of ropivacaine 0.2% with sufentanil 0.5 mcg/ml (CEA; 3-5 ml/h) and a caudal patient-controlled epidural analgesia (PCEA; 3-5 ml/h + bolus of 5 ml/30 min, mixture ropivacaine 0.2% / sufentanil 0.5 mcg/ml) for 3 days when more than 6 segments are involved. When 6 or less segments are involved, only one PCEA is administered (7-10 ml/h + bolus of 5-7 ml/30 min) for 3 days.The child also receives paracetamol (90 mg/kg/day orally) and diclofenac (max 3 mg/kg/ day orally).

When the epidural catheters are removed (day 3 postoperatively), oxycontin (2 x 10 mg, 2 weeks) and, if necessary, oxynorm (6 x 5 mg orally, 2 weeks) is started. Paracetamol is continued (60 mg/kg/day orally, 3 weeks), and celecoxib (orally, 3 weeks) is started as postoperative pain medication (instead of diclofenac). Sometimes, when the child has a lot of muscle pain postoperatively, diazepam is administered.

5.2 Use of co-intervention: *Not applicable*

5.3 Escape medication: *Not applicable*

6. INVESTIGATIONAL PRODUCT: *Not applicable*

The product tested in the present RCT is the sVRE. This mobile app aims to inform participants about the environment of, and procedures in, the operating room. According to the MEDDEV 2.12/6, clinical information systems are not qualified as medical devices[16]. Moreover, the software used in the sVRE app does not perform an action on data[16]. Therefore, this section is not applicable. More information on sVRE is provided in section 5.1.

6.1 Name and description of investigational product(s)

6.2 Summary of findings from non-clinical studies

6.3 Summary of findings from clinical studies

6.4 Summary of known and potential risks and benefits

6.5 Description and justification of route of administration and dosage

6.6 Dosages, dosage modifications and method of administration

6.7 Preparation and labelling of Investigational Medicinal Product

6.8 Drug accountability

7. NON-INVESTIGATIONAL PRODUCT: *Not applicable*

7.1 Name and description of non-investigational product(s)

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

Table 1 (page 24) provides an schematic overview of all outcome measurements.

8.1.1 Main study parameter/endpoint

The primary outcome of this study is postoperative pain upon awakening from anaesthesia (T3). Pain will be assessed with the *Faces, Legs, Activity, Cry, Consolability scale* (FLACC)[17] as an observational measurement of postoperative pain upon awakening from anaesthesia (T3). The FLACC includes behavioural items related to pain that can be scored from 0 (no painful behaviour present; i.e. no cry) to 2 (painful behaviour present, i.e. crying steadily). The total scores range from 0 (no pain) to 10 (a lot of pain). The scale was originally developed and proven valid and reliable for infants and children aged 2 months to 7 years[17]. Two systematic reviews showed that it can be used in older children and adolescents, although psychometric evaluation in this age group is limited[18, 19]. Therefore, this assessment is used as a primary outcome for the (A)TE patients.

For adolescents undergoing surgery for scoliosis, the *Faces Pain Scale* (FPS) will be the primary outcome. The FPS ranges from 0 (no pain at all) to 10 (worst imaginable pain). The FPS has been shown a reliable instrument for the assessment of pain by means of self-report in children[20].

Both scores, the FLACC and the FPS will be assessed for all participants. The FPS will be asked as soon as the participant is able to answer this question.

8.1.2 Secondary study parameters/endpoints

Postoperative analgesics use is a secondary endpoint of this trial. Data will be collected from medical records (analgesics given during hospitalization) and via a questionnaire for the parents (analgesics use at home). Parents will be asked whether their child used the prescribed analgesics or if the child used more or less analgesics. The parents from participants who underwent scoliosis surgery will receive a pain medication diary to keep track of the medication use for answering these questions.

Another secondary endpoint is pre-operative anxiety. The *modified Yale Preoperative Anxiety Scale* (mYPAS)[21] will be used to observe anxiety during induction of anaesthesia. This instrument has been translated from English to Dutch and has already been used in two previous research projects of our research team. The mYPAS has good reliability and validity[21, 22].

Anxiety will also be assessed by using a global score (single score), the *Numeric Rating Scale* (NRS). In this study the NRS consist of a 100 mm horizontal line with two behavioural extremes: 'no anxiety or fear at all' versus 'the worst possible anxiety or fear'. The NRS is a reliable instrument to score state anxiety[23].

In addition, compliance to the induction of anaesthesia is a secondary endpoint. Compliance will be measured with the *Induction Compliance Checklist (ICC)*[24]. The ICC is an observational scale that includes several categories of behaviour that can occur during induction (e.g. "Turns head away from mask"). The total score is the number of categories checked and range from 0 (perfect compliance) to 11 (poor behavioural compliance).

The user experience will be assessed with a self-developed questionnaire. Participants are asked whether they have used the app, how often they used it, whether their parents used it, what the aim of the app was, which grade they would give the app and whether they would advise a friend to use the app.

Sleep will be assessed with the *Patient Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance item bank* [25]. The sleep disturbance item bank consists of 15 items and gives an overview of a participant's sleep problems All items are rated on a 5-point Likert scale from 1 (not at all or never) to 5 (very much or always). Scores can be transformed to T-scores via the official Health Measures scoring service tool. T-scores are anchored on the US general population, with a mean of 50 and a standard deviation of 10. Higher scores represent more sleep problems. Psychometric testing of the Dutch items showed good reliability and validity[26]. For children aged 6 and 7 years, a parent proxy of the PROMIS Sleep Disturbance scale will be used. For children aged 8 years and older, a self-report children's version of the PROMIS Sleep Disturbance scale will be used.

8.1.3 Other study parameters (if applicable)

We will investigate whether the following factors influence smartphone VR effectivity:

Medical outcomes including type of surgery, ASA score, analgesic use and length of hospital stay will be derived from the child's medical file.

Socio-demographic data such as sex and age of the child, presence of brothers/sisters who have been operated, socioeconomic status and the number of prior surgeries of the child will be collected in a baseline questionnaire completed by the parent.

8.2 Randomisation, blinding and treatment allocation

Paediatric patients (aged 6 up to 18 years) undergoing (A)TE or scoliosis surgery, between January 2023 and December 2023 will be randomly assigned to:

a) sVRE intervention

b) CAU: recommended to watch an informative movie at home

Patients will be randomly allocated to the treatment (sVRE) or control (CAU) group on a 1:1 ratio through computer based, block wise randomization per surgery type. Participants will be stratified to scoliosis surgery and age (6-12 years and 13-18 years). The key table connecting allocation number to treatment group is kept in a password protected file and is completed by the research assistant. The research psychologist conducting the measurements will have no access to the file. The sVRE intervention will take place at home via a smartphone application. The psychologist who assesses the child's state anxiety is blinded to the group assignment. This way, blinding for the treatment allocation will be guaranteed. Parents and children in both groups will be asked not to discuss their treatment allocation with the anaesthetist, nurse, or research psychologist.

8.3 Study procedures

For more information on the recruitment and consent procedure, see section 11.2. If the patient and/or parents/guardians have signed informed consent, the baseline assessment will take place at home on a secure website (LimeSurvey via Gemstracker; T0). After that, patients are randomized into one of the two groups: sVRE or CAU.

There will be six moments of assessment:

1. Baseline, approximately one week before surgery (T0).
2. Prior to entering the surgery room (T1).
3. During induction of anaesthesia, in the operating room (T2).
4. Postoperatively, in the recovery room (T3).
5. Five days postoperatively (T4).
6. Twenty-one days postoperatively (T5; only for participants who underwent scoliosis surgery).

T0 and T4 include questionnaires for the child and parent, which will be assessed at home on a secure website. If applicable, T5 includes an online questionnaire for the parent and returning the pain medication diary. T1 and T3 include FPS on pain and NRS on anxiety, which will be verbally assessed by the research psychologist. T1 also includes a questionnaire about the user experience, which will be completed on paper. The observational assessment at T2 and T3 are performed by the research psychologist.

8.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

8.4.1 Specific criteria for withdrawal: *Not applicable*

8.5 Replacement of individual subjects after withdrawal: *Not applicable*

8.6 Follow-up of subjects withdrawn from treatment: *Not applicable*

8.7 Premature termination of the study: *Not applicable*

Table 1. Assessment of key and secondary outcomes and other variables

Instrument/Variable	About	Moment	Informant
Key outcomes			
Faces Pain Scale (FPS)	Child's Postoperative pain	T3	C
Faces, Legs, Activity, Cry, Consolability scale (FLACC)	Child's Postoperative pain	T3	R
Secondary outcomes			
Faces Pain Scale (FPS)	Child's Pain	T0, T1, T4	C
Numeric Rating Scale (NRS) Anxiety	Child's Situational Anxiety	T0, T1, T3, T4	C
Modified Yale Preoperative Anxiety Scale (mYPAS)	Child's Situational Anxiety	T2	R
Induction Compliance Checklist (ICC)	Compliance during induction of Anaesthesia	T2	R
Child's Medical Record/ self-developed questionnaire	Use of analgesics and health care	T3, T4, T5	R, P
PROMIS Sleep Disturbance	Child's Sleep	T0, T4	C
State-Trait Anxiety Inventory (STAI)	Parental Situational Anxiety	T1	P
Self-developed questionnaire	User experience	T1	C
Other variables (predictors)			
Sex, age, SES	Child's Sociodemographics	T0	P
Type of surgery, Number of prior surgeries	Child's Medical Data	T0	R

R = Research psychologist, **P** = Parent, **C** = Child

T0 = Approximately one weeks before surgery (online assessment at home, before the children are randomized)

T1 = Assessment prior to going to the operating room

T2 = Assessment in the operating room during induction of anaesthesia

T3 = Postoperative assessment in the recovery room. The FPS and FLACC are assessed at three moments in the recovery room: upon awakening, 10 minutes after awakening and at discharge. For the scoliosis patients, the NRS will also be assessed during the first 72 hours after the operation, three times a day on the intensive care unit.

T4 = Five days after surgery (online assessment at home).

T5 = twenty-one days after surgery (online assessment at home).

9. SAFETY REPORTING

9.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study. The intervention under investigation is a virtual reality experience. The risks of virtual reality are negligible. Therefore, we anticipate a low occurrence of AEs related to the intervention. All AEs related to the sVRE will be recorded by the investigator or his staff. Adverse events related to surgery will not be recorded and reported by the investigator.

9.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAE:

- Prolongation of hospitalisation after surgery. (A)TE is day care surgery. A maximum of five days of hospitalisation is normal after scoliosis surgery. All events of prolongation of hospitalisation will be collected and reported in the annual progress report.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs): *Not applicable*

9.3 Annual safety report: *Not applicable*

9.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

9.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]: *Not applicable*

10. STATISTICAL ANALYSIS

Data will be analysed using the Statistical Package for the Social Sciences (SPSS).

Minor missing data include missing values on individual survey items. We will work with online questionnaire completion with obligatory answer fields to minimize minor missing data. In case minor missing data occurs despite this effort, we will impute individual items according to the manual of the questionnaire.

The primary analysis will be conducted using an intention-to-treat basis. All patients recruited into the study will be included in this analysis. Patients will be analysed within the group to which they were randomized, irrespective of what care they received. Additional explorative analyses will be done on a 'per protocol' basis.

In general, descriptive statistics will be computed for outcome variables, potential covariates and demographic variables. Bivariate analyses will be undertaken to explore associations between outcome and potentially confounding variables (e.g. age, sex, baseline pain, preoperative anxiety, type of surgery and number of prior surgeries) using correlations (for continuous variables) and Chi-square tests (for categorical variables).

All analyses will be performed separately per surgery type, i.e. (A)TE or scoliosis surgery.

10.1 Primary study parameter(s)

To test the efficacy of sVRE, we will compare the sVRE group to the CAU group. The primary outcome is the child's pain score upon awakening after anaesthesia (T3) measured with the FPS (continuous score). A repeated measures analysis will be conducted with child pain at T0, T1, T3, and T4 (FPS) as within variable, group (VRE versus CAU) as between variable, and age as covariates. For observed child pain at T3 (FLACC), ANOVA will be performed with group as independent variable (sVRE versus CAU). In case of confounding variables, an ANCOVA will be used with the confounding variables as covariates.

10.2 Secondary study parameter(s)

The main secondary outcomes are analgesics use, child anxiety, compliance, user experience, and sleep. For analgesics use at T4 and T5, observed child anxiety at T2 (mYPAS), compliance at T2, and the user experience at T1, ANOVAs will be performed with group as independent variable (sVRE versus CAU) , and age as covariates. In case of confounding variables, an ANCOVA will be used with the confounding variables as covariates. A repeated measures analysis will be conducted with child anxiety at T0, T1, T3, and T4 (NRS) as within variable and group (VRE versus CAU) as between variable. A

similar analysis will be conducted with sleep problems at T0 and T4 as within variable. The p-values will be adjusted for multiple testing.

10.3 Other study parameters

To identify medical or psychological moderators for treatment response to sVRE, we will perform exploratory linear regression analyses with child pain at T3 and child anxiety at T2 as dependent variables. Predictor variables that will be examined are SES, age, sex, preoperative child and parent anxiety, and preoperative sleep problems.

10.4 Interim analysis: *Not applicable*

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki, as amended on the 64th World Medical Association General Assembly in Fortaleza in October 2013, in accordance with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations, and Acts (Code of conduct relating to expressions of objection by minors participating in medical research)[27].

11.2 Recruitment and consent

Patients/parents and professionals will be informed about this project in an early stage for optimal recruitment of patients.

(Adeno)tonsillectomy

The ear, nose, throat specialist will briefly inform eligible patients and their parents about the study. They will ask them if they would like to receive more information about the study by phone. These patients and their parents/guardians will be informed about the study by phone by a member of the research team of Maasstad Ziekenhuis. It will be explicitly stated that participation is completely voluntary and that, if patients decide not to participate, this will not have any consequences for their medical treatment. If they are interested in the study, paediatric patients and their parents will receive the brochure “Medisch Wetenschappelijk onderzoek” and a PIF through mail. The PIF will give a thorough understanding of the purpose and nature of the study. Questions about the study can be discussed in a planned follow-up call with a member of the research team. If parents/guardians and children are willing to participate, the informed consent will be signed during this planned phone call. Participants are asked to return the signed informed consent to the research team Maasstad Ziekenhuis with a return envelope.

Scoliosis

The orthopaedist will briefly inform eligible patients and their parents about the study. They will ask them if they would like to receive more information about the study by phone. These patients and their parents/guardians will be informed about the study by phone by the research psychologist. It will be explicitly stated that participation is completely voluntary and that, if patients decide not to participate, this will not have any consequences for their medical treatment. If they are interested in the study, paediatric patients and their parents will receive the brochure “Medisch Wetenschappelijk onderzoek” and a PIF through mail.

The PIF will give a thorough understanding of the purpose and nature of the study. Questions about the study can be discussed by contacting a member of the research team.

If parents/guardians and children are willing to participate, we will make an appointment with the child and parents 1 week before surgery. On this day, the child and parents visit the hospital for pre-operative screening. During this study visit, they are asked to sign signed informed consent.

All participants

For patients younger than 12 years, written consent will be obtained from their parents/guardians. For patients who are 12-15 years of age, written informed consent will be obtained from both the patient and the parents/guardians. Both parents/guardians are obligated to sign informed consent for their child up to and including 15 years of age. For patients who are 16-18 years of age, written informed consent will be obtained from the patient. The parent/guardian who completes the parent questionnaires will also provide written informed consent for the parent participation, i.e. completion of parent questionnaires. After signing the informed consent, participants will receive the link to the online questionnaires and the 3D glasses when participants are randomized to the sVRE group.

11.3 Objection by minors or incapacitated subjects (if applicable)

We will adhere to the Paediatric Association Of The Netherlands (NVK) code of conduct for dealing with subjects' expressions of objection in the course of the research[27].

11.4 Benefits and risks assessment, group relatedness

This study will assess the efficacy or sVRE. We hypothesize that sVRE will be significantly more efficacious than CAU on children's pain scores and pain medication use post-surgery, as well as on secondary outcomes. Moreover, we hypothesize that children with unfavourable predictor variables will benefit more from sVRE.

If children will be allocated to the CAU group, no harm is done. The children who are randomized to the sVRE condition will wear plastic VR glasses to use the sVRE application. Since this VRE is performed at home, there is a risk that children run into tables, chairs, or other furniture. To limit this risk, parents and children are instructed to only use the sVRE intervention when an adult/guardian is present. Moreover, it cannot be ruled out that some children will become stressed and anxious during the VR. If this is the case, parents are instructed to immediately terminate the sVRE procedure and comfort the child.

The only potential burden for parents and children are the short assessments. The burden for *children* is minimal, as they only rate their pain and anxiety on a FPS and NRS, respectively, and complete a questionnaire on the user experience and sleep (participants aged 8 years or older). The burden for *parents* is also minimal, as they only fill out a number of questionnaires.

If parents or children at any time during the study state that they are in need for acute psychosocial care, or if the research psychologist identifies an acute need for psychosocial care, adequate referral will be arranged.

11.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO. The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study. The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

11.6 Incentives: *Not applicable*

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

The handling of patient material and data will comply with the General Data Protection Regulation (GDPR; in Dutch: Algemene verordening Gegevensbescherming (AVG)). All study data will be handled confidentially and coded with a unique study number. Only the research team (i.e. principal investigators, researcher) involved in this study will be able to identify the participants. The research team, monitor and Inspectie van Gezondheidszorg en Jeugd will have access to the data.

Data will be recorded on a case report form (CRF), which will be managed and checked by the researcher. These data will be entered in a computer system for subsequent tabulation and statistical analysis. Data will be stored during the study period. If patients and their parents give permission, this information will be stored for a period of 15 years.

12.2 Monitoring and Quality Assurance

Monitoring of the study will be done by the Erasmus MC and will take place once a year. During the monitoring the following will be monitored:

1) study documents and agreements;
2) patient inflow, consent, compliance, and Source Document Verification (SDV);
3) patient safety;
4) the investigational intervention (VRE);
5) the study procedures.

See the monitoring plan (K6) for more information.

12.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

12.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

12.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

12.6 Public disclosure and publication policy

Results of this study will be disclosed unreservedly. The results will be presented on national and international conferences and in national and international medical journals, within the scope of the target group, namely: anaesthesiologists, paediatricians, and paediatric psychologists/psychiatrists. The sponsors of this study will not have any influence on data analysis and on publication of results.

This trial will be registered as a clinical trial in the public trial registry before the first patient is recruited.

13. STRUCTURED RISK ANALYSIS: Not applicable

13.1 Potential issues of concern

13.2 Synthesis

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