CLINICAL INVESTIGATION PLAN (CIP)

Efficacy of Virtual Reality Distraction on Procedural Anxiety in Adolescents Undergoing Epidural Placement for Pectus Surgery: An Open-Label Prospective Randomized Controlled Trial. GDW 2026-03

Virtual Reality to reduce anxiety during Thoracic Epidural placement.

Version number: v *3.0* – Date *30/09/2026*

Clinical Investigation number: S71981

Single Identification Number (SIN): *[SIN Nr]*

Sponsor

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Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities. No disclosure should take place without written authorization from the Sponsor.

LIST OF PARTICIPATING SITES

List Of Participating Sites	**Principal Investigator**
University Hospitals Leuven	Geertrui Dewinter, MD, PhD

SIGNATURES

Title: Efficacy of Virtual Reality Distraction on Procedural Anxiety in Adolescents Undergoing Epidural Placement for Pectus Surgery: An Open-Label Prospective Randomized Controlled Trial. GDW 2026-03

CIP: Virtual Reality to reduce anxiety during Thoracic Epidural placement.

The undersigned confirm that the following CIP has been acknowledged and accepted and that they agree to conduct the Investigation in compliance with the approved CIP (and any subsequent amendments if applicable) and will adhere to the principles outlined in the Declaration of Helsinki, applicable Good Clinical Practices and regulations (e.g., the EU Medical Device Regulation 2017/745 (MDR), EU General Data Protection Regulation 2016/679 (GDPR)) and ISO 14155:2020), the appropriate local legislation(s) and all other applicable legal and regulatory requirements as amended. The most stringent requirements, guidelines or regulations must always be followed.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the Investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the Investigation publicly available through publication or other dissemination tools, in accordance with this CIP without any unnecessary delay and that an honest accurate and transparent account of the Investigation will be given; and that any discrepancies from the Investigation as planned in this CIP will be explained.

Coordinating Investigator

Geertrui Dewinter

.....	.....	.....
Name & Title	Signature	Date

Principal Investigator (Participating Site) *(in case of monocentric Trial, the Principal Investigator is the same as the Coordinating Investigator)*

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If the intervention demonstrates clinically meaningful benefit and is feasible within institutional resources, the VR distraction protocol will be considered for integration into routine peri-procedural care. Participants will not be denied access to VR in future procedures at our institution should it become part of standard practice. The Declaration of Helsinki (most recent version) and European and Belgian regulations require that every research involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study. 32

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LIST OF ABBREVIATIONS

Abbreviation	Definition
(e)CRF	(electronic) Case Report Form
ADE	Adverse Device Effect
AE	Adverse Event
AESI	Adverse Event of Special Interest
CA	Competent Authority
CI	Coordinating Investigator
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CM	Concomitant Medication
DD	Device Deficiency
DMP	Data Management Plan
DPA	Data Processing Annex
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ERAS	Enhanced Recovery After Surgery
EUDAMED	European Database for Medical Devices
FPFV	First Patient First Visit
GCP	Good Clinical Practice (latest version of ICH E6)
GDPR	EU General Data Protection Regulation 2016/679
IB	Investigator's Brochure
ICF	Informed Consent Form
IFU	Instructions For Use
IMD	Investigational Medical Device
ISF	Investigator Site File
LPLV	Last Patient Last Visit
MDR	EU Medical Device Regulation 2017/745
NRS	Numeric rating scale
PACU	Postanaesthesia care unit
PCEA	Patient controlled epidural anaesthesia
PI	Principal Investigator (Participating Site)
PRO	Patient Reported Outcome
SADE	Serious Adverse Device Effect

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SIN	Single Identification Number
SOP	Standard Operating Procedure
SoC	Standard of Care
TMF	Trial master File
TE	Thoracic epidural
TEA	Thoracic epidural analgesia
VAS	Visual Analogue score
VR	Virtual Reality
ZBV-k	Zelf-Beoordelings-Vragenlijst-kinderen

FUNDING AND THIRD PARTIES

Funder or service provider	Type of Support
NA	NA

ROLES AND RESPONSIBILITIES

The Principal Investigator (PI) is responsible for the conduct of the Investigation at his/her Participating Site, and for protecting the rights, safety and well-being of the participants. As such the PI must ensure adequate supervision of the Investigation conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Investigation-related duties. The PI will ensure that adequate training is provided and documented for all Investigation staff, prior to conducting assigned Investigation-related activities.

It is the CI's responsibility to supervise the general conduct (e.g., study progress, communication, CIP training and support of the participating sites, annual reporting to the EC, end of Investigation notification(s) and results reporting…) of the Investigation. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in ISO 14155:2020 and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

CIP SYNOPSIS

Title of clinical Investigation («Investigation»)	Efficacy of Virtual Reality Distraction on Procedural Anxiety in Adolescents Undergoing Epidural Placement for Pectus Surgery: An Open-Label Prospective Randomized Controlled Trial. GDW 2026-03
CIP Short Title Acronym	Virtual Reality to reduce anxiety during Thoracic Epidural placement.
Sponsor name	University Hospitals Leuven (UZ Leuven)
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Contact Email CI	Geertrui.dewinter@uzleuven.be
Contact Phone CI	016343407
SIN number	[SIN Nr]
Other public database number	
Medical condition or disease under investigation	Pectus excavatum and carinatum surgery
Study rationale	Anxiety and stress are common prior to thoracic epidural (TEA) placement. Virtual Reality (VR) offers a non-pharmacological adjunct for anxiety management We aim to evaluate immersive VR distraction for reducing procedural anxiety during TEA placement, compared to only Standard of Care (SoC), for adolescents undergoing pectus corrective surgery
Primary objective	The goal of this study is to evaluate if VR distraction can reduce procedural anxiety/stress during TEA placement.
Secondary objective(s)	Improve quality of recovery and patient satisfaction, and reduce rescue sedation medication.
Clinical Investigation Design	Single center open-label prospective randomized interventional trial.
Endpoints	Primary: Subjective Anxiety/stress measured by the Visual analogue scale (VAS) from 0 (no anxiety/distress) and 100 (extreme anxiety/distress) immediately after placement of the TEA. Secondary endpoints: - Rescue sedation medication during TEA placement: dose of Midazolam in mg - TEA placement anxiety (NRS) assessed by the physician performing the epidural and the assisting nurse and accompanying parent, reflecting their perception of the patient's anxiety - Pre and post TEA placement anxiety questionnaire (ZBV-k) - Efficacy of epidural placement: Time and number of attempts - Post TEA placement patient satisfaction and pain score (NRS)
Sample Size	39 in each group, total of 78 patients

IMD	Virtual Reality Bliss DTx device.
Comparator device(s)	None
Maximum duration of treatment and Follow Up of a Participant	1h
Anticipate First Patient First Visit (FPFV)	Screening during preoperative consultation with first patient visit September 2026
Anticipate Last Patient Last Visit (LPLV)	Based on 60 Pectus corrections per year, with 50 meeting the inclusion criteria we expected that this study will be completed by 31 August 2028.

STUDY FLOWCHART

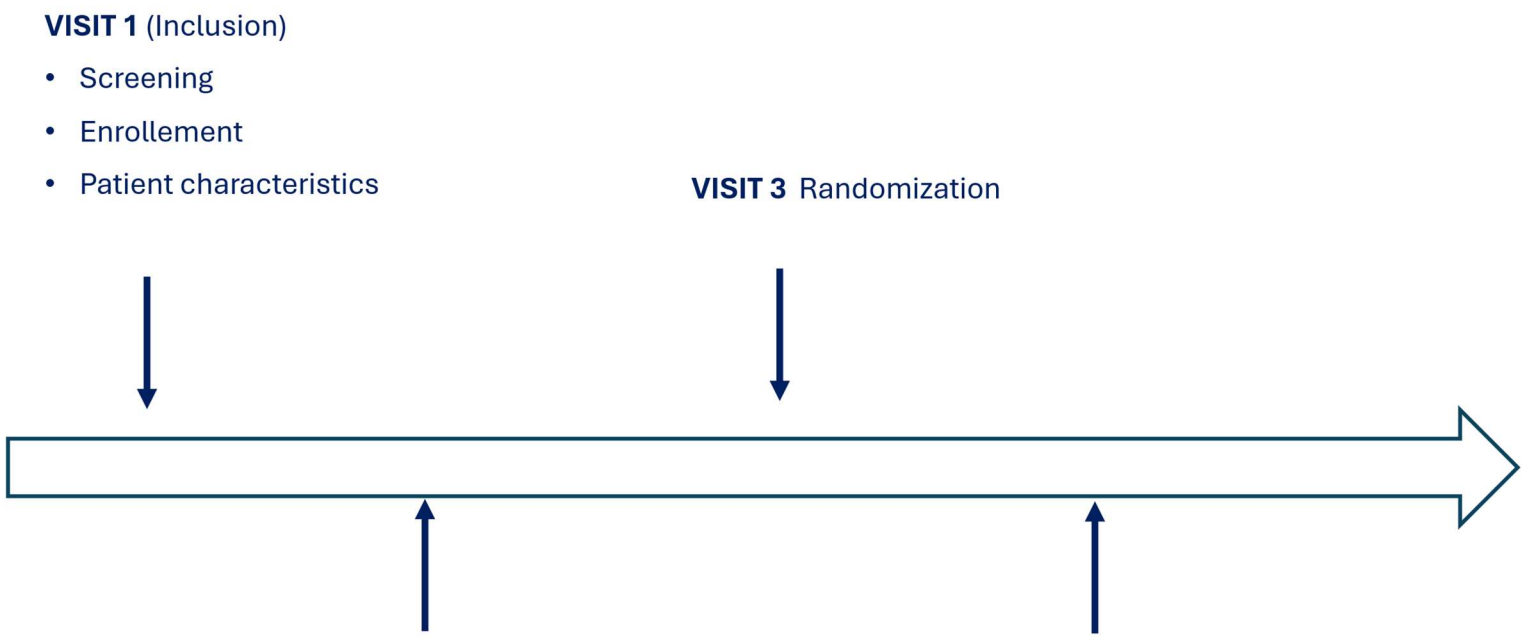
Schedule of Events – Study specific Procedures / Assessments (Figure 1)

Procedures/ Assessment Visits / Contacts	**Screening** Visit 1	**Pre-intervention** Visit 2	**Randomisation** Visit 3	**Post Intervention** Visit 4
Timing (weeks)	Preoperative	Baseline	Pre TEA procedure	Post TEA-procedure
Visit Window (days)	-28 to -1 days	30 (± 15min) before TEA procedure	5 min (±5 min) before TEA procedure	10 min (±5 min) after TEA procedure
Informed consent[1]	X [1]			
Inclusion / Exclusion criteria	X	X		
Demographics	X			
Medical, Surgical history	X			
Weigth / Heigth	X	X		
Vital Signs				X
Randomisation			X	
Use of investigational device or control			X	
Anxiety questionnaire (ZBV-k)		x		X
VAS Anxiety child		x		X
NRS Anxiety parent[2]		x		X
NRS Anxiety nurse[2]		x		X
NRS Anxiety physician[2]		x		X
Post TEA placement satisfaction score (NRS)				X
Post TEA placement Pain score (NRS)				X
Ease of TEA insertion				X
Use of rescue medication				X
Serious) Adverse event (S)(AE) assessment				

1 : Informed Consent be obtained prior to performing any other Trial-related procedures

[2] reflecting the perception of the patient's anxiety

Timeline visits (Figure 1)



1 Background and Rationale

Pectus Excavatum and Carinatum are congenital chest wall deformities requiring surgical correction (Nuss or Ravitch procedures) to improve cardiopulmonary function or address cosmetic concerns. These procedures involve chest wall expansion and tissue disruption resulting in significant postoperative pain.[1] Effective postoperative pain management is crucial, and Enhanced Recovery After Surgery (ERAS) pathways recommend thoracic epidural analgesia (TEA) or paravertebral blockade to facilitate recovery. In adolescents (13-19 years) TEA is frequently placed while the patient is awake or only lightly sedated, yet many of these patients experience substantial anxiety and procedural distress.[2] Stress, an emotional, physical, and physiological reaction of the body to internal or external triggers, is a well-recognized risk factor for adverse mental health outcomes, and adolescents are particularly vulnerable.[3] Preoperative anxiety is reported in up to 67% of pediatric surgical patients and is associated with increased pain perception, more challenging procedural conditions and a higher demand for sedation.[4] Elevated anxiety frequently prompts additional pharmacological sedation, which carries risks such as respiratory depression, extended monitoring requirements, suboptimal positioning during TEA placement and vasovagal syncope. Negative psychological states are consistently linked to poorer surgical outcomes, whereas positive patient experiences enhance recovery, improve analgesic effectiveness and contribute to overall safety patient safety. Addressing procedural anxiety in adolescents undergoing TEA placement is therefore a critical component of perioperative care.

Virtual reality (VR) technology is a promising non-pharmacological intervention for anxiety management and procedural pain control, grounded in the Gate Control Theory of Pain. By delivering immersive, multisensory experience, VR introduces competing non-nociceptive input that can attenuate the transmission of pain, anxiety and distress signals during procedures. Functional magnetic resonance imaging data have demonstrated that VR experiences are associated with significant reductions in pain-related neural activity, including decreased activation in the anterior cingulate cortex, insula, and primary sensory cortices.[5] Randomized trials have demonstrated that VR can effectively reduce procedural anxiety, but to our knowledge, its application during TEA placement in adolescents has not been investigated.[6]

The aim of this trial is to evaluate whether immersive VR distraction can reduce procedural anxiety/distress during TEA placement in adolescents undergoing corrective surgery for pectus deformities.

2 Objectives and Design

2.1 Study objectives and hypotheses

The objective of this study is to reduce anxiety/distress during TEA placement, assessed using the visual analogue scale (VAS) for anxiety score before and after TEA placement. We hypothesize that the use of VR technology compared to standard care (no VR device) will reduce anxiety/distress during the placement of TEA.

2.2 Primary Endpoints

Subjective Anxiety/stress measured by the VAS from 0 (no anxiety/distress) and 100mm (extreme anxiety/distress)immediately after placement of the TEA.

2.3 Secondary Endpoints

- TEA independent anxiety assessments by the physician performing the epidural, the assisting nurse and accompanying parent, reflecting their perception of the patient's anxiety (NRS).
- Pre and post TEA placement anxiety questionnaire from the patient (ZBV-k)

- Rescue sedation medication during TEA placement: dose of Midazolam in mg
- Efficacy of epidural placement: Time and number of attempts
- Post-TEA placement patient satisfaction (NRS) (from 0-10, 0=not satisfied and 10=very satisfied)
- Pain score TEA placement NRS from 0-10, 0=no pain and 10=worst pain))

2.4 Design of the Clinical Investigation

Single center, open label, prospective, randomized controlled trial. In this trial, we will investigate the effect of a VR device on anxiety/distress during the placement of TE. Patients will be randomized to the VR-group or control group (standard of care group). (flowchart, figure 2)

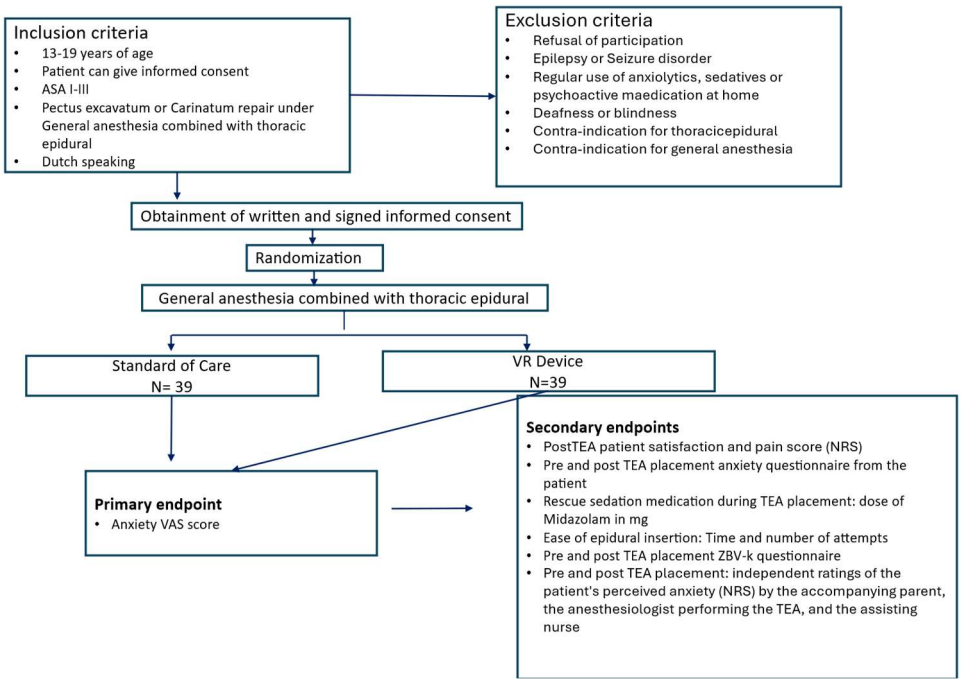


Figure 2: Flowchart

2.5 Justification for the design of the Investigation

The rationale for using this device (Bliss DTx) is to shift management of preoperative anxiety from pharmacological treatments (anxiolytics or sedatives) to non-pharmacological interventions utilizing a VR headset.

2.6 Expected Duration of the Investigation

Following consent, the patients will be randomized prior to surgery in the preparation room where the TEA is placed and the VR device (Bliss DTx) will be used. Following placement of the TEA patient's pain, anxiety and satisfaction scores will be assessed. The studies ends when the patient is transferred to the operating room.

The end of the Investigation is defined as Last Patient Last Visit (LPLV). The CI shall notify the end of the Investigation to the EC within 15 days. The CI will submit a final report with the results of the Investigation, including any publications/abstracts, within one year of the end of the clinical investigation or within three months in case of an early termination. In absence of EUDAMED, the Clinical Investigation Report (CIR) shall be submitted to the involved EC.

The Sponsor, EC or authorized regulatory authority can decide to halt or prematurely terminate the Investigation when new information becomes available whereby the rights, safety and well-being of participants can no longer be assured, when the integrity of the Investigation has been compromised, or when the scientific value of the Investigation becomes obsolete and/or unjustifiable. In case the Sponsor decides to temporary halt or prematurely end the Investigation, or to close a Participating Site in case of major non-compliance and/or critical safety issues, the Sponsor will notify the concerned EC within 15 days of early termination or temporary halt, providing a justification of the event. In the event that the sponsor has temporarily halted or early terminated the Investigation on safety grounds, the Sponsor will inform the EC within 24 hours of the event. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC will be followed.

Circumstances requiring premature treatment interruption or discontinuation of the Investigation, include but are not limited to:

- Safety concerns related to IMD or unacceptable intolerability

3 Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this Investigation have to meet **all** of the following criteria:

1. Voluntary written informed assent of the minor participant and consent of their legally authorized representative or voluntary written informed consent of the adult participant has been obtained prior to any screening procedures
2. Between 13 & 19 years of age at the time of signing the Informed Consent Form (ICF)
3. Scheduled for elective Pectus Excavatum or Carinatum repair (Nuss/Ravitch) with planned Thoracic Epidural Analgesia (TEA).
4. ASA I-III
5. Proficiency in Dutch to allow self-assessment via VAS-Anxiety.

All participants that are considered for Investigation participation per the above criteria, will be documented via applicable log forms in Investigator Site File (including Screen Failures).

3.2 Exclusion criteria

Participants eligible for this Investigation must **not** meet any of the following criteria:

1. Patient has history of Epilepsy or Seizure Disorder
2. Regular use of anxiolytics, sedatives, or psychoactive medication at home.
3. Deafness or blindness preventing VR engagement or VAS self-assessment.
4. Known contraindication to TEA (e.g., coagulopathy) or refusal of TEA.
5. Urgent or emergency surgery.

Participants who meet one or more of the above exclusion criteria **must not proceed** to be enrolled/randomized in the Trial and will be identified via applicable log forms in Investigator Site File.

4 Study Procedures

4.1 Selection of Participants / Recruitment

Potential participants will be identified and recruited during patient consultations. No additional recruitment material (such as for example flyers, social media advertising, audio/video recordings) will be used.

4.2 Investigation assessments and procedures

Trial procedures and their timing are summarized in the Study Flowchart.

4.2.1 Participant consent and withdrawal of consent

The Investigation will be conducted only on the basis of prior informed assent of the minor participant and consent of their legally authorized representative or voluntary written informed consent of the adult participant (s). As such, no Investigation-related procedures will be conducted prior to obtaining written informed assent and/or consent from potential participants.

The process for obtaining and documenting initial and continued informed consent from potential participants will be conducted in accordance with ISO 14155:2020, applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) will be retained/archived in the ISF and will not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the CIP section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the Investigation for any reason at any time. The participant's request to withdraw from the Investigation must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the participant's medical record.

Study data collected before withdrawal can be used in the study. No new study data will be collected after withdrawal of the participant.

4.2.2 Randomization Procedure

Randomization

Patients will be randomized using a computer-generated permuted block randomization sequence to VR-device (interventional group) versus standard care alone (control group) (variable block-size, 1:1 allocation). Allocation concealment will be ensured by enclosing assignments in sealed, opaque, sequentially numbered envelopes which will be opened before surgery at the preparation room.
The anesthetist, nurses and all the other attendees cannot be blinded to the group allocation. The data-collection team and statistical team will be kept blinded.

A randomization list will be prepared by the Sponsor's designated staff, not involved in recruiting participants, medical care, drug administration or follow-up.

4.2.3 Other Investigation assessments and procedures

- **Control group:** Patients allocated to the control group will receive standard care. Upon arrival in the operating room preparation area, baseline anxiety will be assessed using the Zelf-Beoordelings-Vragenlijst voor Kinderen (ZBV-K), a validated Dutch translation of the State-Trait Anxiety Inventory for Children (STAIC). In addition, the patient's current anxiety will be assessed using a Numeric Rating Scale (NRS; 0–10) by the accompanying parent, the anesthesiologist performing the thoracic epidural analgesia (TEA), and the assisting nurse, with the latter three providing independent ratings of the patient's perceived anxiety. An intravenous catheter will then be inserted, after which the anesthesiologist will explain the TEA procedure and position the patient for epidural placement. Immediately following successful TEA placement, the patient's anxiety will again be assessed using both the ZBV-K and the patient-reported NRS, together with independent NRS ratings of the patient's perceived anxiety by the accompanying parent, anesthesiologist, and assisting nurse. Patient's pain and satisfaction scores will also be recorded using an NRS.

Intervention group: Patients allocated to the intervention group will receive immersive virtual reality (VR) in addition to standard care. Upon arrival in the operating room

preparation area, baseline anxiety will be assessed using the Zelf-Beoordelings-Vragenlijst voor Kinderen (ZBV-K), a validated Dutch translation of the State-Trait Anxiety Inventory for Children (STAIC). In addition, the patient's current anxiety will be assessed using a Numeric Rating Scale (NRS; 0–10) by the patient, the accompanying parent, the anesthesiologist performing the thoracic epidural analgesia (TEA), and the assisting nurse, with the latter three providing independent ratings of the patient's perceived anxiety. The virtual reality (VR) device (Figure 3) will then be explained to the patient and fitted, allowing sufficient time for familiarization with the virtual environment. These virtual environments are designed to reduce anxiety and distract patients during painful medical procedures.

The four virtual worlds available in this system are:

1. **Nohara:** A dreamy and peaceful walk through the countryside.
2. **Kaitei:** A relaxing exploration of the ocean floor and the underwater world.
3. **Uchuu:** A calming spacewalk among the stars and planets.
4. **Mori:** A magical and dreamlike journey through a peaceful forest.

While the patient remains immersed in VR, an intravenous catheter will be inserted, after which the anesthesiologist will explain the TEA procedure and position the patient for epidural placement. Verbal communication with the patient will be maintained throughout the intervention. The VR intervention will continue during TEA placement and will be discontinued immediately after successful epidural catheter placement. Following TEA placement, the patient's anxiety will again be assessed using both the ZBV-K and the patient-reported NRS, together with independent NRS ratings of the patient's perceived anxiety by the accompanying parent, anesthesiologist, and assisting nurse. Patient's pain and satisfaction will also be assessed using an NRS.



Figure 3: Virtual Reality device: Bliss DTx

Rescue treatment: The current standard approach for managing anxiety or distress during TEA placement is the administration of anxiolytics, typically midazolam. Rescue anxiolysis may be provided upon patient request or at the clinician's discretion to ensure comfort. Midazolam will be titrated, and its clinical effects, as well as potential side events, will be continuously monitored. The need and the total administered dose of rescues anxiolytics will be documented.

4.3 Premature discontinuation

Participants may voluntarily discontinue from the Investigation treatment and/or prematurely end their participation in the Investigation for any reason at any time. In such case the Investigator must make a reasonable effort reassure the patient and continue TEA placement using the standard of care procedure.

The Investigator may also decide at any time during the course of the Investigation, to temporarily interrupt or permanently discontinue the treatment if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

In any such case of early termination and/or treatment interruption/discontinuation, the Investigator will continue to closely monitor the participant's condition and ensure adequate medical care and follow-up.

5 Investigational Medical Device (IMD)

Investigational Medical Device Name (& company brand)	**CE mark** (Y – N - NA)	**Used within Indication** (Y or N)	**Manufacturer of the device**
Bliss DTx	Y	Y	Neo DTx

5.1 Intended use

The Bliss DTx device of Neo DTx is an immersive solution designed to support patients before, during, and after painful and/or anxiety provoking medical procedures. It is used as an adjunct to or replacement for pharmacological agents (sedatives). The solution immerses patients in auditory and visual environments that engage their capacities and induce an altered state of consciousness, significantly reducing perceived pain levels.

5.2 Identification and description of the IMD

Bliss DTx is a medical device for the reduction of pain during and after painful medical procedures. and anxiety before.
The VR device will be in contact with skin of the face of the patient, there will be no contact with body fluids. (see appendix 3: appendix 1(Instructions for use for Bliss DTx Medical device, Class I) and 2 (EU Declaration of Conformity)

5.3 Device Accountability

The trial investigators are accountable for the device, for the handling and storage of it.

6 Safety reporting

6.1 Definitions

The definitions and reporting requirements adopted in this CIP are based on the MDR, ISO 14155:2020 and the MDCG 2020-10/1 European guideline and the vigilance provisions.

6.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons, in the context of a clinical investigation, whether or not related to the investigational medical device.

Note:
a. This definition includes events related that are anticipated as well as unanticipated events
b. This definition includes events occurring in the context of a clinical investigation related to the investigational device, the comparator or the procedures involved.

6.1.2 Serious Adverse Event (SAE)

A SAE is any adverse event that led to any of the following:

a) death,
b) serious deterioration in health of the subject, that resulted in any of the following:
   - life-threatening illness or injury,

- permanent impairment of a body structure or a body function,
- hospitalisation or prolongation of patient hospitalisation,
- medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- chronic disease,

c) foetal distress, foetal death or a congenital physical or mental impairment or birth defect.

6.1.3 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device or a comparator.

6.1.4 Serious Adverse Device Effect (SADE)

A SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

An Unanticipated Serious Adverse Device Effect is any SADE of which the nature, severity or outcome is not consistent with the reference safety information.

6.1.5 Device Deficiency (DD)

A DD is any inadequacy in the identity, quality, durability, reliability, safety or performance of an investigational device, including malfunction, use errors or inadequacy in information supplied by the manufacturer.

6.1.6 Adverse Events of Special Interest (AESI)

The following events should be reported within the same timelines as SAEs:

Not applicable

6.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness, unless the pre-existing condition appears to be worsened).
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first investigation-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the investigation:

- Not applicable

Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first trial-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol therapy administration. However, hospitalisation or prolonged hospitalisation for a complication of therapy administration will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

6.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events, whether reported by the patient or noted by trial staff, will be recorded in the patient's medical record and in the (e)CRF within a reasonable time after becoming aware. If available, the diagnosis should be reported on the AE form, rather than the individual signs or symptoms. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs using separate AE forms.

The following minimum information should be recorded for each AE:

- AE description

- start and stop date of the AE

- severity

- seriousness

- causality assessment to the Investigational Medical Device (IMD) and/or study procedures

- outcome

6.3.1 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.

- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**

Not related	Relationship to the device, comparator or procedures can be excluded when: - the event has no temporal relationship with the use of the investigational device, or the procedures related to application of the investigational device - the serious adverse event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible; - the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious adverse event; - the event involves a body-site or an organ that cannot be affected by the device or procedure; - the serious adverse event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors); - the event does not depend on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

Possible	The relationship with the use of the investigational device or comparator, or the relationship with procedures, is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed, or no information has been obtained should also be classified as possible.
Probable	The relationship with the use of the investigational device or comparator, or the relationship with procedures, seems relevant and/or the event cannot be reasonably explained by another cause.
Causal relationship	The serious adverse event is associated with the investigational device, comparator or with procedures beyond reasonable doubt when: - the event is a known side effect of the product category the device belongs to or of similar devices and procedures; - the event has a temporal relationship with investigational device use/application or procedures; - the event involves a body-site or organ that • the investigational device or procedures are applied to; • the investigational device or procedures have an effect on; - the serious adverse event follows a known response pattern to the medical device (if the response pattern is previously known); - the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious adverse event (when clinically feasible); - other possible causes (eg, an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out; - harm to the subject is due to error in use; - the event depends on a false result given by the investigational device used for diagnosis, when applicable; In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious adverse event.

6.3.2 Timelines for reporting

- After informed consent has been obtained but prior to first use of the IMD, only adverse events caused by a study specific procedure should be reported
- After first use of the IMD, adverse events will be reported as follows:
    - All AEs and SAEs related to a study procedure or the IMD, AESIs and Device Deficiencies will be reported until last (follow-up) visit.

All SAEs and AESI as defined in the protocol must be reported to the Sponsor within 24 hours of the trial staff becoming aware of the event. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by code numbers.

SAE details will be reported by the Investigator to the sponsor by completing the SAE form in the (e)CRF

If an authorised Investigator from the reporting site is unavailable, initial reports without causality assessment should be submitted to the Sponsor by a healthcare professional within 24 hours of becoming aware of the SAE, but must be followed-up by medical assessment as soon as possible thereafter.

6.3.3 Follow-up

The Investigator must record follow-up information by updating the patient's medical records and the appropriate forms in the (e)CRF. The worst case severity and seriousness of an event must be kept throughout the trial.

SAE follow-up information should only include new (e.g. corrections or additional) information and must be reported within 24 hours of the Investigator's first knowledge of the information. This is also the case for previously non-serious AEs which subsequently become SAEs.

- All *SAEs* must be followed up until the outcome of the event is 'recovered', 'recovered with sequelae', 'not recovered' (in case of death due to another cause) or 'death' (due to the SAE) and until all related queries have been resolved, or until end of trial (whichever occurs first).
- *Non-serious AEs* must be followed up until the patient's last study visit, and/or until all related queries have been resolved.

SAEs after the end of the investigation: If the Investigator becomes aware of an SAE with suspected causal relationship to the IMD or experiment after the subject has ended the investigation, the Investigator should report this SAE within the same timelines as for SAEs during the investigation.

6.3.4 Death

All deaths will be reported without delay to the sponsor (irrespective of whether the death is related to disease progression, the IMD, study procedure or is an unrelated event). If considered a reportable event, the sponsor must notify the EC(s) and CA(s) for materiovigilance as soon as possible after becoming aware.

6.4 Recording and reporting of Device Deficiencies

Each Device Deficiency must be documented by the Investigator in the source documents and reported to the Sponsor on a Device Deficiency form.

If the Device Deficiency leads to the occurrence of a (S)ADE, the (S)ADE must also be reported by the Investigator to the Sponsor on the appropriate forms and within the specified timelines.

6.5 Reporting requirements to Ethics Committees (EC's)

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs, AESIs and Device Deficiencies against medical experience to identify and expeditiously communicate possible new safety findings to Investigators and applicable EC's based on applicable legislation.

6.5.1 Sponsor's reporting of Serious Adverse Events and Device Deficiencies

The Sponsor is responsible to report to the EC's where the clinical investigation has commenced:

- Any SAE that has a **causal** relationship with the device, the comparator or the investigation procedure* or where such causal relationship is reasonably possible;
- Any Device Deficiency that might have led to a SAE if:
    a) Appropriate action had not been taken or,
    b) Intervention had not occurred or,
    c) If circumstances had been less fortunate
- New findings/update in relation to already reported reportable events.

**a study-specific procedure related to the use of the investigational device or comparator (outside the standard of care).*

These 'reportable events' must be reported within the following timelines:

- A reportable event which results in imminent risk of death, serious injury, or serious illness that requires prompt remedial action for other patients/subjects, users or other persons or a new finding to it must be reported immediately, but not later than **2 calendar days** after awareness by the sponsor of a new reportable event or of new information in relation with an already reported event.

- Any other reportable event or a new finding/update to it must be reported immediately, but not later than **7 calendar days** following the date of awareness by the sponsor of the new reportable event or of new information in relation with an already reported event.

6.6 Sponsor's reporting of Materiovigilance to Competent Authorities (CA's)

Serious incidents or potential serious incidents related to the use of a CE marked device used within its intended purpose should be reported to the CA according to the materiovigilance provisions.

The following should be notified as soon as possible:

- Any dysfunction or any change of the characteristics and/or performance of a device, and any inadequacy in the labelling or instructions, which might lead to or have led to death or serious relapse in the state of health of a patient, a user or a third party.
- Any incident that might have resulted in one of the following clinical implications:
  - death
  - life-threatening injury
  - permanent or significant impairment of a body structure or a body function
  - hospitalisation or prolongation of patient hospitalization
  - need for medical or surgical intervention
  - congenital physical or mental impairment, foetal distress or foetal death
  - delayed or incorrect diagnosis or treatment
  - transfusion of improper materials

This also includes any risk of a serious incident that could be prevented by the actions and interventions of the involved persons.

6.7 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AE	AE form	sponsor	Within 7 calender days
	SAE	SAE form	sponsor	asap, but no later than 3 calendar days after awareness
	Device Deficiency (DD)	DD form + AE/SAE form (if applicable)	sponsor	Within 7 calender days (exception: within 3 calendar days if considered reportable event)
	death	SAE form	sponsor	asap
Sponsor	all reportable events (of all participating sites)	EU SAE report form (excel)[1]	- Ethics Committee(s) -	asap, but no later than - 2 calendar days (in case of risk of death or serious injury/illness that requires prompt remedial action for other patients, users or other persons) - 7 calendar days (all other reportable events)

	Materiovigilance	Meddev report form[2]	- CA for Belgium -> FAGG: via mail to vigilance.meddev@fagg-afmps.be -	asap

[1]The SAE report form in excel format can be downloaded from the following web page: https://ec.europa.eu/health/sites/health/files/md_sector/docs/md_mdcg_2020-10-2_guidance_safety_report_form_en.xlsx?web=1

[2]The Meddev report form can be downloaded form the following web page: https://www.fagg.be/sites/default/files/content/notification_incident_nl_0.pdf

6.8 Data Safety Monitoring Board (DSMB)

After a thorough evaluation of the potential risks to Investigation participants and considering the nature, design and complexity of the clinical Investigation, the Sponsor has determined not to establish a DSMB. This decision is grounded in our conclusion that this is a low risk clinical Investigation in which the IMD has a CE mark and is used within indication. In addition, the potential risks associated to the study procedures and protocol design are comparable to that of standard medical care.

The Investigation is committed to ensuring the safety and well-being of all participants at all times by adhering to the latest version of ISO 14155:2020 and other relevant and applicable standards and legislations.

7 Statistics and Data Analysis

Statistical analysis will be performed in accordance with ICH E9; a detailed description of the analysis is provided in the study-specific Statistical Analysis Plan (SAP). ICH E3 and E8 will guide the structure and content of the clinical study report.

We hypothesize that the addition of the VR device (Bliss DTx) compared to standard care will reduce the anxiety/distress during TEA placement in adolescents undergoing pectus corrective surgery.

7.1 Sample Size Determination

To detect a between-group difference of 1 point (clinically meaningful difference) in postoperative anxiety (VR vs control), assuming:

The number of patients has been calculated to have at least 80% power to show a reduction of 1point in the mean VAS score. In an unpublished series of 13 patients the mean VAS score equalled 6.15 (SD=1.46). Based on a two-sided t-test with alpha equal 0.05, 35 patients per group are needed (70 in total). In order to compensate for possible drop-outs, we will increase the amount of patients to 78. Drop-outs may occur if the virtual reality is unavailable due to technical problems with the device.

A total of 70 patients (35per group) are required. Allowing for an anticipated 10% attrition rate, the total sample size will be increased to 78 patients (39per group).

7.2 Statistical Analysis

7.2.1 Efficacy Analysis

Endpoint	Statistical Analysis Methods
Primary	The primary endpoint is postprocedural anxiety score measured using VAS scale , analyzed using analysis of covariance (ANCOVA) with adjustment for baseline (pre-procedural) anxiety. In pilot observational data (n=13), the standard deviation (SD) of

	postoperative anxiety was 1.69 points, and the correlation between baseline and postoperative anxiety was r = 0.51. Using this correlation, the residual variance under ANCOVA is reduced by a factor of ($1 - r^2$), corresponding to an effective SD of approximately 1.46.
Secondary	- PostTEA patient satisfaction and pain score (NRS) - Rescue sedation medication during TEA placement: dose of Midazolam in mg, - Ease of epidural insertion (duration from needle insertion in minutes, number of attempts), - Pre and post TEA placement: independent ratings of the patient's perceived anxiety (NRS) by the accompanying parent, the anesthesiologist performing the TEA, and the assisting nurse - pre and post TEA placement ZBV-k questionnaire We will not perform corrections for multiple testing and these analyses are to be considered exploratory.

Other Analysis

7.3 Interim Analysis and Final Database Lock

No interim analysis

8 Data handling

Data handling and data flows for the Investigation are summarized below and will be described in more detail in the Investigation-specific Data Management Plan (DMP).

8.1 Data Collection Tools and Source Document Identification

8.1.1 Operational aspects

Data collection, handling, processing and transfer for the purpose of this Investigation will be performed in compliance with applicable regulations, guidelines for clinical trials and internal procedures, as follows:

8.1.1.1 Data collection

Source data will be collected and recorded in the participant's files/medical records.

If applicable, worksheets may be used for capturing some specific data in order to facilitate completion of the (e)CRF. Any such worksheets will become part of the participant's source documentation and will be filed together with or as part of the medical records (during but also following completion of the Investigation).

It remains the responsibility of the Investigator to check that all data relating to the Investigation, as specified in the CIP, are entered into the (e)CRF in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Investigation data will be transcribed from the source records (i.e., participant's medical file or study-specific source data worksheets) into an (e)CRF from RedCap by study staff. Transcription to the (e)CRF will be done as soon as possible after a participant visit and in a pseudonymized manner using a unique identifier assigned by the Sponsor.

8.1.1.2 Data Validation

All data relating to the Investigation must be prepared and validated by the Investigator. Any (e)CRF entries, corrections and alterations must be made by the Investigator or other authorized study staff.

Proper audit trails must be available to demonstrate the validity of the Investigation data collected. This includes historical records of original data entries, by whom and when the data was entered, as well as detailed records of any corrections or additions made to the original data entry (i.e., who made the correction/addition, when and why), without obliterating the original data entry information.

8.1.1.3 Data Management

The Study Data Manager will perform extensive consistency checks on the received data. Queries will be issued in case of inconsistencies in accordance with internal procedures. A DMP will be developed to map data flows, data validation measures that will be taken, how (interim) database lock(s) will be managed and, as applicable, the role and responsibilities of the DSMB.

8.1.1.4 Data Transfer

Any participant records or datasets that are transferred to the Sponsor or any partners of the Sponsor will contain the study-specific participant identifier only; participant names or any information which would make the participant identifiable will not be transferred. All pseudonymized data relating to the Investigation must be transmitted in a secure manner to the Sponsor or any partners of the Sponsor (see 8.1.2. legal requirements).

8.1.2 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the GDPR, and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Study staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Investigation disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Investigation as described in this CIP. The collection, processing and disclosure of personal data, such as participant health and medical information, is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each participant, and will maintain a TMF/ISF containing all study documents, as specified in ISO 14155:2020 Annex E entitled "*Essential clinical investigation documents",* and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the GDPR).

8.2 Audits and Inspections

The Investigator will permit direct access to study data and documents for the purpose of monitoring, audits and/or inspections by authorized entities, such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such, (e)CRFs, source records and other study related documentation (e.g., ISF, TMF, pharmacy records, etc.) must be kept current, complete and accurate at all times.

8.3 Monitoring

In accordance with ISO 14155:2020, the Sponsor is responsible for monitoring the Investigation to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the study procedures have been followed as

shown in the approved CIP, and that relevant study data have been collected and reported in a manner that assures data integrity.

UZ Leuven Clinical Trial Center (CTC) performs a risk analysis to determine the monitoring strategy. Based on this risk assessment, the clinical trial was classified as 'low risk' as the potential risks associated to study procedures and protocol design are comparable to that of standard medical care since the IMD has a CE label and is used within indication.

Based on the above risk assessment and as permitted by GCP, the Sponsor of the trial accepts the minimal risks associated with this trial and determines that monitoring activities (as defined by GCP) by a qualified individual, independent of the study team, is not necessary as it will provide little or no added value in protecting the safety of trial participants and assuring the integrity of collected trial data. Nonetheless, the UZ Leuven study team will take all possible measures to assure the quality and integrity of trial data and to safeguard the safety and wellbeing of trial participants, in accordance with the requirements set out in GCP and ISO:14155.

8.4 Archiving

As specified in ISO 14155:2020 section 8.6, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Clinical Investigation Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Investigation.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Investigation.

The Sponsor and Investigator is responsible for archiving study specific documentation (such as but not limited to the CIP, any amendments thereto, the final Clinical Investigation Report (CIR) and the study database), according to ISO 14155:2020. Source data and site-specific study documents (such as but not limited to the original signed ICFs) will be archived by the Participating Site(s) according to local practice, and for a period of at least 10 years after the clinical Investigation with the device in question has ended, or, in the event that the device is subsequently placed on the market, at least 10 years after the last device has been placed on the market.[1] Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

9 Ethical and Regulatory Considerations

9.1 Ethics Committee (EC) review & reports

Before the start of the Investigation, this CIP and other related documents (e.g., ICF, advertisements, IB, etc.) will be submitted for review to the EC for authorization. The Investigation shall not commence until such approval have been obtained and until other relevant essential Investigation documents, such as duly signed contract agreements, evidence of adequate financing etc. are in place..

9.2 Peer review

This protocol has been reviewed by clinicians and nurse practitioners experienced in the regular use of the VR device. The flowchart (Figure 2) has been approved by all parties involved and are part of routine practice. All comments provided during the review process have been incorporated into this final version.

9.3 Regulatory Compliance

The Investigation will be conducted in compliance with the principles outlined in the requirements for the conduct of clinical investigations in the EU, as provided for in the MDR, as applicable, and any subsequent

[1] According to UZ Leuven policy, Study documents will be archived for at least 25 years following termination of Investigation.

amendments, as well as in compliance with ISO 14155:2020, other GxP guidelines, the most recent version of the Declaration of Helsinki, the Belgian law of May 7th, 2004 regarding experiments on the human person (as amended), or the Belgian law of December 22nd, 2020 concerning medical devices, as applicable, the Belgian royal decree of May 18th, 2021 concerning clinical investigations of medical devices, and with the GDPR, the relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd, 2002 on patient rights, and all other applicable legal and regulatory requirements.

9.4 CIP / GCP compliance

The Investigation must be performed in accordance with the CIP, ISO 14155:2020, and applicable regulatory and country-specific requirements. ISO 14155:2020 is an international ethical and scientific quality standard for designing, conducting, recording and reporting clinical investigations that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety and well-being of participants are protected, consistent with the principles that originated in the Declaration of Helsinki, and that the study data are credible, reliable and reproducible.

The Investigator and study team acknowledge and agree that prospective, planned deviations or waivers to the CIP are not permitted under applicable regulations on clinical investigations. However, should there be an accidental CIP- deviation, such deviation shall be adequately documented in the source documents and on the relevant forms and reported to the CI and Sponsor. Deviations should also be reported to the EC as part of the EC's continued review of the Investigation. Protocol deviations which are found to frequently recur, will require (immediate) action. The Investigator acknowledges that such recurring protocol deviations could potentially be classified as a major protocol deviation.

The Investigator is expected to take any immediate action required to protect the safety of any participant included in the Investigation, even if this action represents a deviation from the CIP. In such cases, the Sponsor should be notified of this action and the EC should be informed according to local procedures and regulations.

The Sponsor has performed a risk assessment to reduce anticipated risks with regards to the safety, wellbeing and rights of the participants as well as with regards to the reliability and robustness of the clinical Trial data.

9.5 Data protection and participant confidentiality

The Investigation will be conducted in compliance with the requirements of the GDPR, the relevant Belgian laws implementing the GDPR, including the Belgian Privacy Act of July 30th, 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken to ensure that appropriate protection travels with the data in accordance with the GDPR (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9.6 Insurance

The Sponsor, Participating Site and the Investigator shall have and maintain in full force and effect during the term of this Investigation, and for a reasonable period following termination of the Investigation, adequate insurance coverage for: (i) medical professional and/or medical malpractice liability, and (ii) general liability.

For Belgian Participating Sites

Article 32 of the Belgian Law concerning medical devices dated December 22nd, 2020 applies. Prior to the start of the Investigation, the Sponsor shall enter into an insurance contract in order to adequately cover participants from Belgian Participating Sites in accordance with Article 32 of the said law.

9.7 Amendments

As specified in ISO 14155:2020 section 7.5.1, amendments must not be implemented prior to EC review and/or approval, as applicable. Under emergency circumstances, deviations from the CIP to protect the rights, safety or well-being of human subjects may proceed without prior approval of the sponsor and the EC. Such deviations shall be documented and reported to EC as soon as possible.

In accordance with the Belgian law of December 22nd, 2020 concerning medical devices, the Sponsor may develop a non-substantial amendment at any time during the Investigation. If a substantial amendment is introduced to the CIP, or the documents that supported the original application for the clinical Investigation, authorisation is needed, the Sponsor must submit a valid substantial amendment for approval to the EC. The EC will provide a response in accordance with timelines defined by applicable law. It is the Sponsor's responsibility to assess whether an amendment is substantial or non-substantial. In absence of EUDAMED, local guidelines with regards to notifications and submissions to the concerned EC will be followed.

Amendments to the Investigation are regarded as 'substantial' when they are likely to have a substantial impact on the safety, health or rights of the subjects or on the robustness or reliability of the clinical data generated by the investigation.

https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-10/2010_c82_01/2010_c82_01_en.pdf

9.8 Post-Study activities

10 Research Registration, Dissemination of Results and Publication Policy

If the intervention demonstrates clinically meaningful benefit and is feasible within institutional resources, the VR distraction protocol will be considered for integration into routine peri-procedural care. Participants will not be denied access to VR in future procedures at our institution should it become part of standard practice. The Declaration of Helsinki (most recent version) and European and Belgian regulations require that every research involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study.

In addition, the CI will fulfil its ethical obligation to disseminate and make the research results publicly available. As such, the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results, must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

Publications will be coordinated by the CI. Authorship to publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors, and in accordance with the requirements of the respective medical journal.

11 Intellectual Property

Any know how, inventions, methods, developments, innovations, discoveries and therapies, whether patentable or not, arising from the Investigation or made in the performance of the CIP ("Inventions") shall vest in the Sponsor. If the Investigation is multicentric, the Participating Site, its employees and Investigator(s) shall promptly disclose to the Sponsor any such Inventions. The Sponsor and the Participating Site have expressly agreed that any and all study data as collected and prepared in the

performance of the CIP shall be the sole property of the Sponsor, unless otherwise agreed in the Investigation agreement between the Sponsor and the Participating Site.

12 References

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Appendices

13 Appendix 1: Instruction for use for Bliss DTX Medical Device, Class I

Bliss DTx

Instructions for use for Bliss DTx
Medical device, Class I

The purpose of these instructions for use is to ensure that Bliss DTx is used correctly. Please read this information carefully and follow the instructions it contains.

You should always use Bliss DTx by strictly following the information provided in this leaflet or by your doctor or pharmacist.
Keep this leaflet.
You may need to read it again.
The Neo DTx support team will be happy to answer any questions you may have.

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WHAT BLISS DTX IS AND WHEN TO USE IT

Bliss DTx is part of the Bliss DTx solution for pain and anxiety management.
Class of this medical device
Bliss DTx is a class I reusable active medical device.
Bliss DTx is a medical device compliant with regulation (EU) 2017/745 art.2.

Intended use

Bliss DTx is a medical device for reducing pain and anxiety before, during and after painful medical procedures.

Bliss DTx may only be used with the support of a healthcare professional trained in the use of this medical device. Bliss DTx is intended for use in patients aged 12 and over.

The Bliss DTx device can be used alone or in addition to a local anaesthetic, in the following applications (this list is not exhaustive):
- during diagnostic or sampling procedures such as endoscopies, punctures (pleural, ascites, lumbar, myelogram) and biopsies.
- during surgical procedures in oncology (catheter port insertion), urology (bladder surgery), vascular surgery (varicose vein surgery), orthopaedics (knee surgery, hand surgery, hallux valgus), oral surgery (wisdom tooth avulsion), etc.
- during painful post-surgical care (re-dressing, burns, mobilisation, etc.).

HOW TO USE BLISS DTX

Instructions for proper use

The Bliss DTx software is installed on a virtual reality headset.

It is recommended to use Bliss DTx in a quiet environment to ensure best results from the medical device.

Before using the virtual reality headset, check the battery level. There must be sufficient charge to prevent any sudden stoppage during the session.

If using Bliss DTx away from a power source, make sure

you have a spare external battery.

Positioning Before Launching the Experience:

The device offers 6 starting positions:

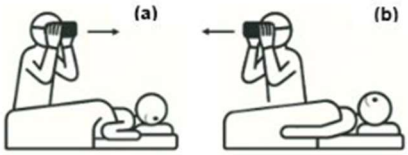
(1) **Lateral decubitus:** lying on the side.
(2) **Prone position:** lying face down.
(3) **Seated position with anterior tilt (~30°):** seated, slightly leaning forward.
(4) **Neutral seated position:** seated upright.
(5) **Seated position with posterior tilt (~30°):** seated, slightly leaning backward.
(6) **Supine position:** lying on the back.

Before launching the experience, select the position corresponding to the patient's posture.

- For positions (1) (3) (4) (5), the "Recenter" button can be used to adjust the patient's viewing angle after the experience has started.
- For the prone (2) and supine (6) positions, the recentering function is not available.

The healthcare professional must therefore:

1. Position the virtual reality headset in the correct orientation, corresponding to the patient's orientation, before launching the experience.
   a) Select the **Prone position (2)**.
   Stand laterally to the patient as shown in diagram (a).
   b) Select the **Supine position (6)** in the application.
   Stand laterally to the patient as shown in diagram (b).
2. Look **straight ahead**, then **adjust the headset by holding it in front of the eyes while maintaining this position**.
3. Then launch the program without using the "Recenter" function.
4. Once the program has started, **place the headset on the patient's head**.



A misalignment at startup may result in an incorrect perception of the virtual environment.

Place the virtual reality headset on the head in the patient's field of vision a few minutes before the medical procedure.

Then place the headphones over the patient's ears.

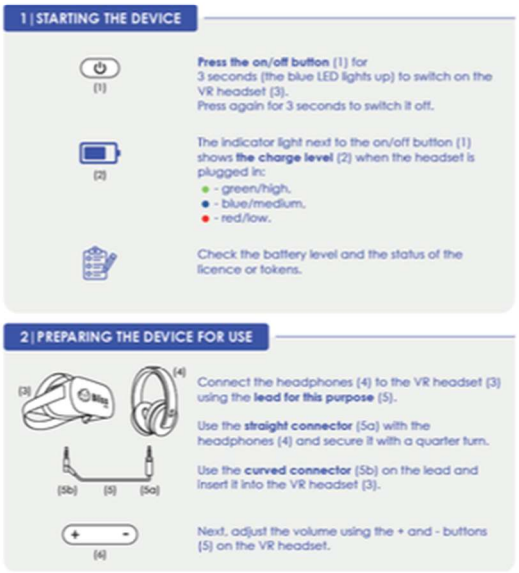
At the end of the session, to avoid a sudden shutdown, first press the "exit the environment" button, then remove the headphones, and finally the virtual reality headset.

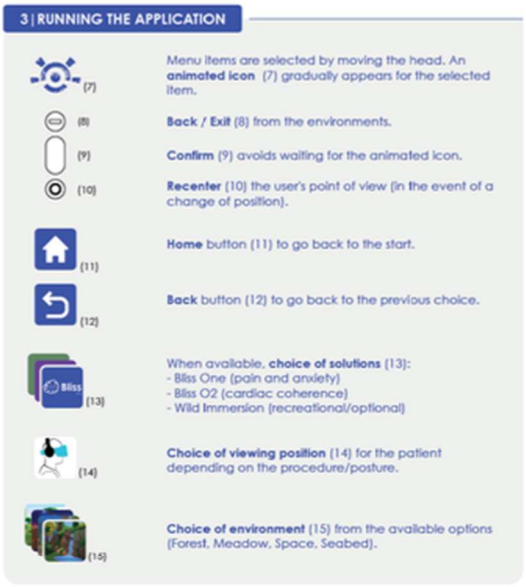
Treatment duration

The different durations of the virtual reality programmes that come with Bliss DTx are pre-programmed.
There is no limit to the frequency of sessions.
The period of use of Bliss DTx is defined by the medical procedure and the associated protocol. The recommended period of use is around 45 minutes. However, this may be extended up to 2 hours with medical advice and depending on the medical procedure being performed.

Environment for use

Should it be necessary to interrupt a Bliss DTx session, the healthcare professional should move around quietly and speak softly, to maintain the effects of Bliss DTx and then resume therapy under optimal conditions.





Note:
The Recenter function (10) depends on the headset model used, which can be identified by its color:
• Pico G3+ headset (white, see diagram): Recentering by a brief press on the "Recenter" button

(< 1 second).

• Pico G2 headset (black, see diagram): Recentering by pressing and holding the "Recenter" button for approximately 3 seconds.



Pico G3+ headset *Pico G2 headset*

POSSIBLE ADVERSE EFFECTS

Bliss DTx may cause slight discomfort at the start of the session, as the patient adapts to the medical device. This possibility of discomfort should be explained to the patient.

Adverse effects linked to the use of Bliss DTx are limited to the three symptoms that may be caused by the virtual reality headset: headaches, dizziness and nausea. These are infrequent and can be dealt with by temporarily interrupting the virtual reality session.

If the patient experiences any of the above symptoms:

Until the above symptoms have completely disappeared, it is recommended not to drive, operate machinery or undertake visually or physically demanding and potentially hazardous activities (i.e. any activity during which the occurrence of such symptoms could result in death, bodily injury or damage to property), or any activities requiring a good sense of balance or hand-eye coordination (sports or cycling, etc.). Wait several hours after complete resolution of the symptoms before resuming a session that has been interrupted due to the onset of the symptoms described.

If you experience any side effects from using Bliss DTx, please email support@neodtx.com.

Any serious incident relating to the use of the product must be reported to the manufacturer and to the responsible authority in the country in which the patient and/or user is established.

There are currently no known interactions.

In addition to these warnings, no adverse effects have been reported since the market launch of Bliss DTx.

WARNINGS AND CONTRAINDICATIONS

The use of Bliss DTx needs to be explained by trained staff to ensure its analgesic/anxiolytic effects are produced.

For people with impaired vision, the use of Bliss DTx must be approved by a healthcare professional.
Bliss DTx is not recommended for patients with poor vision and/or hearing (glaucoma, very young patients under the age of 6), or for patients with photosensitivity and/or epilepsy.

Driving vehicles and using machines

If the patient is driving after a session with Bliss DTx, make sure that they are sufficiently alert. You can check the patient's state of alertness using the Glasgow scale provided at the end of the leaflet. If the Glasgow score is 15, the patient is sufficiently alert.

Precautions for use and handling

⚠ Keep away from open flames.

HOW TO STORE AND CARE FOR BLISS DTX

Do not expose Bliss DTx to a source of heat or bright light, as this may burn the screen, which will have to be replaced.
Particular care and attention must be paid to the headset lenses.
The virtual reality headset and the headphones used with Bliss DTx are fully cleanable and disinfectable. After each use, clean with disinfectant wipes such as surface safe wipes or similar (standard 14476).

Cleaning the virtual reality headset:
- Use a special microfibre lens cloth moistened with a little water to clean the optical lenses.
- Use the disinfectant wipes to gently wipe down the foam padding on the headset and the areas around it in contact with the skin, until the surface is slightly damp and can dry for at least 5 minutes. Leave to dry

before use.

Cleaning the headphones:
- Use the disinfectant wipes to gently wipe down the headset pads and straps until the surface is slightly damp and can dry for at least 5 minutes. Leave to dry before use.

MINIMUM SYSTEM REQUIREMENTS

Bliss DTx must only be used with the virtual reality headset and headphones supplied with Bliss DTx. In the event of malfunction or damage to either of these products, please contact NEO DTX.

MANUFACTURER

NEO DTX
874 Route de Change
72530 YVRE-L'EVEQUE, FRANCE
Email : support@neodtx.com

SOFTWARE VERSION

The current version of the Bliss DTx software is V3.

INFORMATION UPDATE

Version v8
07-12-2025

OTHER INFORMATION

Disposal

Products used in combination with Bliss DTx must be disposed of in accordance with the applicable regulations for waste electrical and electronic equipment at the end of its life.

If you have any technical questions, please email support@neodtx.com.

If you would like to receive a printed copy of these instructions for use free of charge, please send a request to the Technical Support e-mail address given above. We will send you the paper version within 7 calendar days.

CE 14-01-2026

UK CA

MD

MEANING OF SYMBOLS

Manufacturer

MD Medical device

14 Appendix 2: European Declaration of Conformity for CE Marking

Docusign Envelope ID: 445D010F-C5C8-434F-9465-50A6267A6209

European Declaration of Conformity for CE Marking

Doc No: DOC-BLISS-EN
Date: 5 December 2025
Revision: J

Manufacturer: **Neo DTx**
Address: **874 Route de Changé**
72530 Yvré-L'Évêque, France
Manufacturer's SRN: **FR-MF-000048664**

We, Neo DTx, declare that this declaration of conformity has been issued under our sole responsibility:

Name of the medical device: **Bliss DTx**
Medical device version: **V4**

EMDN classification: **V9099 – Miscellaneous medical devices not included in any category – other**
IUD-ID: **03701780800008**
Basic IUD-ID: **37017808BlissDTxBY**
Device class: **Class I** (in accordance with Annex VIII of Regulation (EU) 2017/745, **Rule 11**).

Intended use: Bliss DTx is a medical device for the reduction of pain and anxiety before, during and after painful medical procedures.

This statement complies with the provisions of Regulation (EU) 2017/745 of 5 May 2017 on medical devices. The technical documentation for the **Bliss DTx** solution has been prepared by **Neo DTx** in accordance with Annexes II and III of Regulation (EU) 2017/745.

Harmonised standards/Technical specifications	EN ISO 15223-1:2021 Medical devices - Symbols for use with information to be supplied by the manufacturer - Part 1: General requirements
	EN ISO 20417:2021 Medical devices - Information to be supplied by the manufacturer
	EN ISO 14971:2019/A11:2021 Medical devices - Application of risk management to medical devices
	EN 62304:2006/A1:2015 Medical device software - Software life cycle processes
	EN 62366-1:2015/A1:2020 Medical devices - Part 1: Application of usability engineering to medical devices
	EN 10993-1:2020 Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process

The list of products used in combination with Bliss DTx is presented in Appendix 1

Place and date: **Yvré-L'Évêque, 5 December 2025**
Name and position: **C. Bouchet, Chair**
Signature

Signé par :
Christine Bouchet
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Docusign Envelope ID: 445D010F-C5C8-434F-9465-50A6267A6209

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Signature

Signé par :
Christine Bouchet
E35A2FAA0C044F5...

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Bliss DTx

EU Declaration of Conformity
Appendix 1

Doc No: DOC-BLISS-EN
Date: 15 September 2025
Revision: J

List of products used in combination

The products listed below are used in combination with Bliss DTx:

Name **Trade name**	**Product** **Product**	**Manufacturer**	**Applicable** **Applicable**
Pico G2 4K virtual reality headset (VR All-In-One Headset)	A7510	Pico Immersive Pte Ltd Room 2101, Shining Tower, No. 35 Xueyuan Road, Haidian District, Beijing, P.R. China	CE marked according to Directive 2014/53/EU
Pico G3 4K Virtual Reality Headset	A7Q10	Qingdao Chuangjian Weilai Technology Co., Ltd Room 401, 4th Floor, Building 3, Qingdao Research Institute, 393 Songling Road, Laoshan District, Qingdao City, Shandong Province, China	CE marked in accordance with Directives 2014/53/EU 2015/863/EU 2009/125/EC
Pico 4 Virtual Reality Headset	A8110		CE marked in accordance with the directives 2014/53/EU 2015/863/EU 2009/125/EC
Focal Listen Wireless® headphones	ESPICAS111-BL001	Focal Focal Jmlab - 108, rue de l'Avenir - 42353 La Talaudière	CE marked in accordance with Directives 2014/53/EU, 2014/35/EU and 2014/30/EU
Focal Headphones Listen Professional			CE marked according to directives 2014/35/EU and 2014/30/EU

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