A multicentre, randomised cross-over equivalence trial investigating knowledge of anatomy following virtual reality or standard teaching in novice anaesthetists

Short Study Title/Acronym: RA Anatomy – VRvST Study

IRAS ID: 356761

CHIEF INVESTIGATOR:

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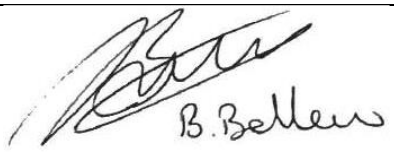
Signature Page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Declaration of Helsinki, the Sponsor's SOPs, and other regulatory requirement.

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 study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies from the study as planned in this protocol will be explained.

This protocol has been written in accordance with the Sponsor's guidance for writing non-CTIMP protocols.

Chief Investigator (CI) Dr Boyne Bellew Consultant Anaesthetist		
Royal National Orthopaedic Hospital NHS Trust (RNOH)	Signature	Date
Principal Investigator (PI) (if different from CI)		
N/A		
N/A	Signature	Date
Sponsor Representative Miss Emily Stimpson Research Management and Governance Lead		
Royal National Orthopaedic Hospital NHS Trust (RNOH)	Signature	Date

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1. LIST OF ABBREVIATIONS

AE	Adverse Event
AR	Adverse Reaction
APR	Annual Progress Report
ASR	Annual Safety Report
CAG	Confidentiality Advisory Group
CI	Chief Investigator
CRF	Case Report Form
DMC	Data Monitoring Committee
GAfREC	Governance Arrangements for Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HRA	Health Research Authority
ICF	Informed Consent Form
ISF	Investigator Site File
ISRCTN	ISRCTN – The UK's Clinical Study Registry
NHS R&D	National Health Service Research & Development
NIMP	Non-Investigational Medicinal Product
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
RCT	Randomised Control Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
VR	Virtual reality

2. STUDY PERSONNEL AND FACILITIES

Chief Investigator (CI): Dr Boyne Bellew
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Phone: 0141 337 2636

3. STUDY SYNOPSIS

Full study title:	A multicentre, randomised cross-over equivalence trial investigating knowledge of anatomy following virtual reality or standard teaching in novice anaesthetists
Short study title:	RA Anatomy – VRvST Study
Chief Investigator:	DR Boyne Bellew
Medical condition/disease under investigation:	Sonoanatomy knowledge using Virtual Reality
Study duration:	24 months
Primary Objective:	Score out of 44 on a validated test of anatomy and sono-anatomy
Secondary Objective:	Before training • Handedness (Edinburgh Handedness Inventory) • Subjective sleepiness (Karolinska scale) • Motor reaction time (Psychomotor Vigilance test) • Attention control (Anti-Saccade test) • Mental rotation (Mental Rotation Task) • Depression Anxiety, Stress (DASS score) • Visual Search Task (Divided Attention) • Knowledge pretraining After training and testing • Knowledge after training session • Acceptability: Client Satisfaction Questionnaire (CSQ-8) • Usability: CyberSickness in Virtual Reality Questionnaire (CSQ-VR) • Immersion: Witmer and Singer Presence Questionnaire • Subjective workload (NASA – TLX scale) • Cognitive Demand Battery (CBD) • Resource use: Calculation of cost differences between learning Modalities
Study population:	Resident anaesthetists
Recruitment Target:	102
Recruitment Window (Months):	6 – 12 months
Methodology:	This is a non-clinical randomised controlled trial of resident anaesthetists undergoing training in regional anaesthesia. Residents will be randomised to one of two groups for each training session day: ▪ Standard anatomical training (Group A) ▪ Virtual reality based anatomical training. (Group B) Then followed by another training day session and participants will enter either standard or VR teaching depending on the previous allocation: ▪ Standard anatomical training (Group B) ▪ Virtual reality based anatomical training. (Group A) Anatomical knowledge will be tested in both groups using an on-line questionnaire developed by the Chief Investigator (CI).
Eligibility criteria:	***Inclusion criteria:***

	1. Anaesthetists that are residents in a recognised Royal College of Anaesthetists (RCoA) training program 2. Anaesthetic training grades (Stage 1 – 3).
	Exclusion criteria: 1. Visual impairment (this does not include wearing glasses/contact lenses) 2. History of severe diseases affecting physical motion or balance 3. History of any drugs that may affect physical motion or balance within 12 hours of the intervention 4. Pregnancy 5. Individuals who had consumed alcohol within 24 h of the intervention. 6. Resident doctors not in a recognised RCOA training program *e.g.* Staff grade anaesthetists.
Study treatment: *(i.e. study intervention if applicable)***:**	
Standard teaching – control **Virtual reality teaching – intervention.**	

4. INTRODUCTION

4.1 BACKGROUND

Regional Anaesthesia competency is difficult to achieve within the Royal College of Anaesthetists' (RCoA's) 2021 curriculum[1]. Standard teaching includes lectures, volunteer scanning and needling practice on plastic phantoms. Cadaver training is limited and expensive.

Knowledge of anatomy relies on 2D drawings and ultrasound images. There is a need to learn 3D anatomy, including its variations, that allows interactive learning similar to that found using a cadaver, but at a distance and at a cheaper price[2].

A potential solution is Virtual Reality - the process of being fully immersed in a computer generated environment[3]. Application of VR to anatomical teaching shows promise to accelerate learning but application has been marred by limited, poor quality research[4]. A systematic review of 15 RCTs and 816 students[5] showed an improvement in knowledge using VR (SMD 95%) = 0.53 (0.09 to 0.97); and high homogeneity (I2= 88%). The review recommended future focus on satisfaction, cost-effectiveness, and adverse reactions. On the other hand, nine (five non-systematic) reviews found a lack of robust evidence[4]. Although realistic immersive systems show face validity, this does not necessarily translate to learning[3]. Moreover, users may fail to perform tasks without guidance, under stress, over the long term and on translation to clinical practice.[3]

There is a clear need to develop innovative ways to ensure training needs are of a high standard and meet the RCOA requirements[1]. From a scientific perspective, it is also important to investigate how individuals learn and retain knowledge, non-technical skills[6] and the complex interactions between cognition, perception and motor control within the immersive environment[7].

4.2 PRE-CLINICAL DATA/CLINICAL DATA

"Overall, the competence-based education model and immersion VR, which represent 2 major advances in our medical education armamentarium, have the potential to improve clinical

performance and increase patient safety. Anaesthesiologists are well positioned to lead the development and adoption of these futuristic educational tools given our risk management mindset and technical affinity."[2]

"It is clear that we need a combination of a bottom- up drive (from clinicians, educators, researchers, developers) complemented by top- down initiatives (organisations, funders, journals) that facilitate work across disciplines, institutions, fields, sectors and countries to build capacity and change perspectives through the use of immersive technologies."[3]

"To clarify to what extent VR, AR, or MR can replace or supplement TAE methods, there is a primary need for addressing issues regarding the definition of each technology and determining which specific TAE methods are used as comparators."[4]

"The finding confirms that VR may act as an efficient way to improve the learners' level of anatomy knowledge. Future research should assess other factors like degree of satisfaction, cost-effectiveness, and adverse reactions when evaluating the teaching effectiveness of VR in anatomy."[5]

4.3 STUDY RATIONALE AND RISK/BENEFIT ANALYSIS

We propose that in order to develop a sound knowledge of anatomy and sono-antomy, virtual reality could be used as an aid to understanding and interpreting 2-D sono-antomical structures. Trainees will have an enhanced learning experience that reinforces the skills required to perform safe regional anaesthesia

Hypothesis: We hypothesise that knowledge of regional nerve anatomy among novice anaesthetists using 3D virtual reality is equivalent to standard teaching.

4.4 MANAGEMENT OF POTENTIAL STUDY RISKS

One potential major weakness is the risk of trainer bias when delivering training. The knowledge test was written by Dr Bellew, and that Dr Bellew and Prof McLeod will be delivering the 'VR training' and 'standard training' arms respectively. The possibility exists for the trainers to bias results by providing test-specific training to one arm, but not the other. To mitigate this risk training packages with specific anatomical areas taught and check lists will be used by an observer to ensure all aspects are taught and/or omitted as per the training package.

Virtual reality is usually regarded as safe to use. There are reports of it causing headache, eyestrain, fatigue, blurred vision and dizziness with prolonged use. These symptoms tend to get better shortly after participants stop using the virtual reality equipment. We will minimise the risk of these symptoms by limiting the use of the virtual reality headset to 2 – 3 x 30-40 minute sessions within an eight-hour period. We will be assessing for these side effects using validated questionnaires. Also, the VR environment will be projected onto a screen for participants if they need to remove the VR equipment.

5. STUDY OBJECTIVES

5.1 PRIMARY OBJECTIVE

Our **primary aim** is to study **knowledge** of anatomy following initial VR teaching compared to standard teaching

Primary end-point: Score out of 44 on a validated test of anatomy and sono-anatomy

5.2 SECONDARY OBJECTIVES

Secondary objectives and end-points:

Before training

- Handedness (Edinburgh Handedness Inventory)
- Subjective sleepiness (Karolinska scale)
- Motor reaction time (Psychomotor Vigilance test)
- Attention control (Anti-Saccade test)
- Mental rotation (Mental Rotation Task)
- Depression Anxiety, Stress (DASS score)
- Visual Search Task (Divided Attention)
- Knowledge pretraining

After training and testing

- Knowledge after each training session
- Acceptability: Client Satisfaction Questionnaire (CSQ-8)
- Usability: CyberSickness in Virtual Reality Questionnaire (CSQ-VR)
- Immersion: Witmer and Singer Presence Questionnaire
- Subjective workload (NASA – TLX scale)
- Cognitive Demand Battery (CBD)
- Resource use: Calculation of cost differences between learning modalities

6. STUDY DESIGN

6.1 OVERALL DESIGN

This is a multicentre, non-clinical randomised cross-over equivalence controlled trial of resident anaesthetists undergoing simulation training in regional anaesthesia. Residents will be randomised to one of two groups for the first training session day:

- Standard anatomical training (Group A)
- Virtual reality based anatomical training. (Group B)

AND participants will then undergo a second training session day 2 – 4 weeks later and will be allocated to a group not previously allocated

- Standard anatomical training (Group B)
- Virtual reality based anatomical training. (Group A)

Experimental design and methods
(Workpackage (WP); Milestone (M); Deliverables (D))

WP 1 Baseline measurements

M 1.1 Confirmation of capacity and capability (C&C) at each site

M 1.2 Inclusion criteria: anaesthetists (non-pregnant) from London, Nottingham, Tayside, Sunderland.

M 1.3 Measure online participant characteristics and psychometric measures (secondary outcomes as above) using web based Inquisit Lab 5 platform (Millisecond Software, Seattle).

D1 Report results.

WP 2 Training and testing

M 2.1 Randomisation Participants will be randomised to one of two groups

- Standard training
- VR based training

M 2.2 Psychometric testing (pre training secondary end points as above)

M 2.3 VR familiarisation

VR training will be preceded by VR familiarisation. Participants will wear Meta Quest 3 VR glasses and learn upper and lower limb anatomy using the 3D Organon package https://www.3dorganon.com/ that also incorporates sono-anatomy related to regional anaesthesia

M 2.4 Training will be structured, last 30 – 40 min and follow the principles of deliberate practice. Training will consist of 1:1 trainer: trainee interaction with feedback either after the VR session or during the standard training session.

Training will cover upper and lower limb blocks, truncal and abdominal blocks. The standard session will consist of a lecture followed by learning on a plastic anatomical model. All training to be provided by Dr Bellew and Prof McLeod at all centres

M 2.5 Testing Knowledge will be tested four occasions and pseudoanonymised using a random code generator.

- Before training
- After training

M 2.6 Questionnaire feedback

- Post-test secondary endpoints as above

D 2.1 Conference paper

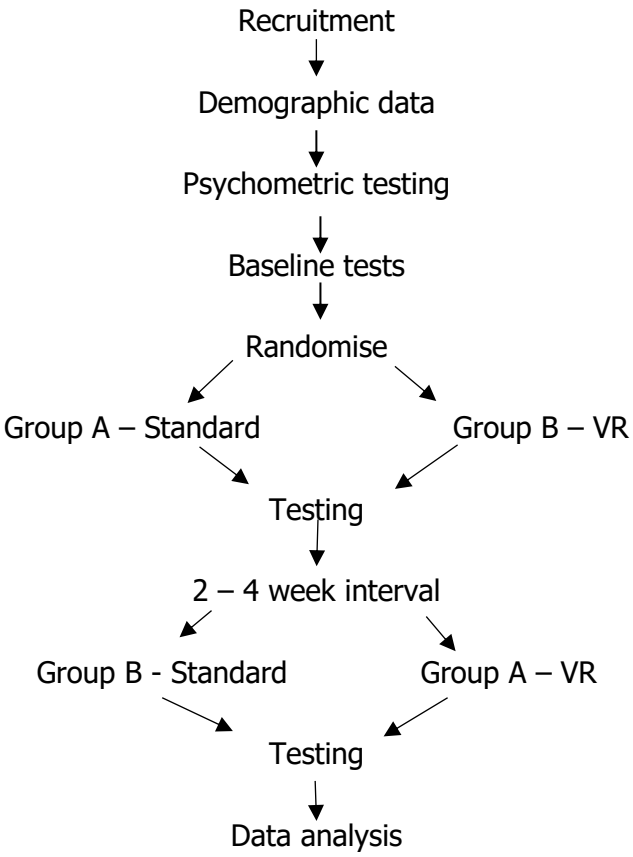
D 2.2 Journal submission

Testing consists of questions involving sono-anatomy video clips of nerve blocks. The tests will be completed on the on-line platform (r)[14] with a built in time limit. Answers will be free-text and marked by two blinded raters. All participants will be allocated a code so that results could be pseudo-anonymised.

6.2 TREATMENT AND RATIONALE

N/A

6.3 SCHEMATIC OF STUDY DESIGN



7. ELIGIBILITY CRITERIA

7.1 INCLUSION CRITERIA

Anaesthetists that are in a recognised Royal College of Anaesthetists (RCoA) training program in the Uk, Anaesthetic training grades (Stage 1 – 3).

7.2 EXCLUSION CRITERIA

- Visual impairment (this does not include wearing glasses/contact lenses)
- History of severe diseases affecting physical motion or balance
- History of any drugs that may affect physical motion or balance within 12 hours of the intervention
- Pregnancy
- Individuals who had consumed alcohol within 24 h of the intervention.

7.3 DISCONTINUATION/WITHDRAWAL OF PARTICIPANTS AND STOPPING RULES

Each participant has the right to withdraw at any time. If a participant withdraws, we will continue to analyse any data already collected, unless they express a wish for any associated data to be destroyed.

8. PARTICIPANT RECRUITMENT PROCESS

Participant recruitment at a site will only commence once the *study* team has ensured that the following approvals/essential documents are in place:

1. Health Research Authority (HRA) approval
2. Local Site Delegation of Duties and Signature Log is completed (if applicable)
3. Confirmation of Capacity and Capability.

All sites participating in the *study* will also be asked to provide a copy of the following:

1. Signed Organisation Information Document (OID) or model agreement, as agreed with the Sponsor
2. Confirmation of Capacity and Capability
3. Sponsor greenlight (if applicable).

Potential participants will be those resident doctors enrolled in a RCoA recognised anaesthetic training program. Participants will be recruited *via* advertised email to anaesthetic departments in the UK, Heads of Schools of training will also be asked to disseminate emails and *via* local messaging groups within the various Schools of anaesthesia.

9. STUDY PROCEDURES

9.1 INFORMED CONSENT

Consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet offered, and time allowed for consideration. Signed participant consent will be obtained. The right of the participant to refuse to participate without giving reasons must be respected. All participants are free to withdraw at any time.

Informed consent will be obtained by the Chief Investigator (CI), Principal Investigator (PI) and/or a nominated deputy as recorded on Sponsor's Delegation of Responsibilities Log locally.

Consent to enter this study will be obtained after a full account has been provided of its nature, purpose, risks, burdens and potential benefits, and the participant has had the opportunity to deliberate. The participant will be allowed to specify the time they wish to spend deliberating, usually up to 24 hours.

Periods shorter than 24 hours will be permitted if the participant feels that further deliberation will not lead to a change in their decision, and provided the person seeking consent is satisfied that the participant has fully retained, understood and deliberated on the information given.

Likewise, periods longer than 24 hours will be permitted should the participant request this. The Investigator or designee will explain that the participants are under no obligation to enter the study and that they can withdraw at any time during the study, without having to give a reason.

A copy of the signed Informed Consent Form (ICF), along with a copy of the most recent approved Participant Information Sheet (PIS) will be given to the study participant. The original signed consent form will be retained at the study site and filed in the Site Investigator File (ISF) / Trial Master File (TMF).

If new safety information results in significant changes to the risk–benefit assessment, the consent form and Participant Information Sheet will be reviewed and updated if necessary. All subjects, including those already enrolled, will be informed of the new information, given a copy

of the revised consent form and PIS and asked to re-consent if they choose to continue in the study.

9.2 RANDOMISATION PROCEDURE

A computer-generated program for random numbers will be used for simple randomization of participants https://www.randomizer.org/

This is a non-clinical randomised controlled trial of resident anaesthetists undergoing simulation training in regional anaesthesia. Residents will be randomised to one of two groups for each training session day:

- Standard anatomical training (Group A)
- Virtual reality based anatomical training. (Group B)

AND followed 2 – 4 weeks later

- Standard anatomical training (Group B)
- Virtual reality based anatomical training. (Group A).

9.3 EMERGENCY UN-BLINDING

N/A

10. STUDY ASSESSMENTS

10.1 SCREENING ASSESSMENTS

Baseline demographic data: Age, Sex, Handedness, Training level, Peripheral nerve block experience.

10.2 BASELINE ASSESSMENTS

Before training

- Handedness (Edinburgh Handedness Inventory)
- Subjective sleepiness (Karolinska scale)
- Motor reaction time (Psychomotor Vigilance test)
- Attention control (Anti-Saccade test)
- Mental rotation (Mental Rotation Task)
- Depression Anxiety, Stress (DASS score)
- Visual Search Task (Divided Attention)
- Knowledge pretraining

10.3 TREATMENT PROCEDURE

After training and testing

- Knowledge after each training session
- Acceptability: Client Satisfaction Questionnaire (CSQ-8)
- Usability: CyberSickness in Virtual Reality Questionnaire (CSQ-VR)
- Immersion: Witmer and Singer Presence Questionnaire
- Subjective workload (NASA – TLX scale)
- Cognitive Demand Battery (CBD)
- Resource use: Calculation of cost differences between learning modalities.

10.4 Subsequent assessments

N/A

10.5 Summary Chart of study assessments

Study schedule of events:

	Recruitment	Pre-baseline	Baseline	2 - 4 weeks
Consent	x			
Psychometrics on-line		x		
Training			x	X
Testing		x	x	X
Post test questionnaires			x	X

11. Methods

11.1 Laboratory Procedures

N/A

11.2 Radiology or any other procedure(s)

N/A

- ***Techniques and Interventions***

Virtual Reality - the process of being fully immersed in a computer-generated environment teaching anatomy.

- ***Tools***

Virtual reality anatomy software: https://www.3dorganon.com/

Virtual reality headset: Metquest 3S: Meta Quest 3S: New mixed reality headset – Shop now | Meta Store

11.3 Definition of the End of Study

The end of the study is the final outcome measure assessments taken from the final study participant.

12. SAFETY REPORTING

12.1 DEFINITION

Adverse Event (AE) — any untoward medical occurrence in a patient or clinical study subject who is administered a treatment and which does not necessarily have a causal relationship with this treatment (*i.e.* any unfavourable or unintended change in the structure (signs), function (symptoms), or chemistry (lab data) in a subject to whom a treatment/study procedure has been administered, including occurrences unrelated to that product/procedure/device).

Serious Adverse Event (SAE) – is defined as an untoward occurrence that:

- Results in death; or
- Is life-threatening (places the subject, in the view of the Investigator, at immediate risk of death)
- Requires hospitalization or prolongation of existing hospitalization (hospitalisation is defined as an inpatient admission, regardless of length of stay; even if it is a precautionary measure for observation; including hospitalisation for an elective procedure, for a pre-existing condition)
- Results in persistent or significant disability or incapacity (substantial disruption of one's ability to conduct normal life functions)
- Consists of a congenital anomaly or birth defect (in offspring of subjects or their parents taking the study drug regardless of time of diagnosis)
- Is otherwise considered medically significant by the investigator.

Important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the outcomes listed in the definition of serious will also be considered serious.

12.2 RECORDING ADVERSE EVENTS (AES)

All Adverse Events (AEs) will be recorded in the hospital notes and Case Report Form (CRF). If the Investigator suspects that the disease has progressed faster due to the administration of the study treatment/procedure, then he/she will report this as an unexpected adverse event to the Sponsor and the REC as detailed in Section 12.6.

12.3 ASSESSMENT OF SAES

Classification and causality of Adverse Events (AEs) will be conducted by local PIs and reviewed by the CI. The CI cannot downgrade the site PI's classification and if there is disagreement which cannot be resolved during formal discussion then the assessment of the site PI will be accepted. The CI, can however, upgrade the seriousness of an event without consultation with the site PI.

12.4 EXPECTED AES

We do not anticipant specific adverse events relating to this non-clinical study of training in anatomical knowledge.

12.5 REPORTING OF SAEs TO THE SPONSOR AND THE REC

The CI is responsible for reporting SAEs to the RIC immediately and/or within 24 hours of becoming aware of the event in accordance with the process outlined below.

An SAE occurring to a research participant will be reported to the Research Ethics Committee (REC) that gave a favorable opinion of the study, the study Sponsor (RNOH RIC) and the local R&D Office where in the opinion of the CI/PI the event was:

- **'Related'**: that is, it resulted from administration of any of the research procedures; and
- **'Unexpected'**: that is, the type of event is not listed in the protocol as an expected occurrence.

Reports of related and unexpected SAEs will be submitted to the REC within 15 days of the CI/PI becoming aware of the event; using the SAE reporting form for non-CTIMPs published on the HRA website and entitled non-CTIMP safety report to REC. The form should be completed in typescript and signed by the Chief Investigator (CI) prior to submission to the REC.

Reports of SAEs in double-blind studies should be un-blinded.

All SAEs that are to be reported to the REC should also be forwarded to the RIC in parallel and must be recorded, signed and dated by the Investigator at site. The RIC accepts study specific or HRA SAE Forms.

Information can be submitted to the RIC in electronic format:

- E-mail: rnoh.rmg@nhs.net

Following submission by the CI, the coordinator of the main REC will acknowledge receipt of safety reports within 30 days. It is the responsibility of the CI and his/her research team to send a copy of the SAE notification and acknowledgement receipt to the RIC.

The research team also has the responsibility to report SAEs occurring in a certain period (28 days) after a patient completes the study. Any SAEs reported to the Investigators during this phase must be documented in the patient's medical notes and submitted *via* an SAE reporting form.

Principal Investigators (PI) at all sites will report all SAEs to the Chief Investigator (CI) who will review and forward such reports within 24 hours to the study Sponsor.

12.6 THE TYPE AND DURATION OF FOLLOW UP

In this non-clinical study we do not anticipant adverse events arising from study procedures. In the event of an unanticipated adverse event each participant will be followed-up on a one-to-one basis by the local PI and/or CI until the event is resolved, in order to ensure safety.

12.9 REPORTING URGENT SAFETY MEASURES

The Sponsor and/or the Investigator may take appropriate urgent safety measures in order to protect the subjects of a clinical study against any immediate hazard to their health or safety. If safety measures are taken, REC approval is not required before the measure is taken.

The Investigator will immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the REC and the study Sponsor of the measures taken and the circumstances giving rise to those measures.

In order to prevent any delays in the reporting timelines the Sponsor has delegated this responsibility to the CI/PI. Therefore, the CI/PI must report any urgent safety measures to the REC directly, and in parallel to the Sponsor. The REC coordinator will acknowledge receipt of urgent safety measures via email.

13. DATA MANAGEMENT AND QUALITY ASSURANCE

13.1 CONFIDENTIALITY

All data will be handled in accordance with the Data Protection Act (2018), General Data Protection Regulation (GDPR) (2018), NHS Caldecott Principles, The UK Policy Framework for Health and Social Care Research, and the condition of the REC approval.

The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. The subject's study Identification Number (ID), will be used for identification.

No data will be shared with any external organisation without appropriate consent and data sharing agreement in place, as applicable.

13.2 DATA COLLECTION TOOL

Case Report Forms (CRF) will be designed by the CI and the final version will be reviewed and discussed with the study Sponsor. All data will be entered legibly in black ink with a ball-point pen. If the Investigator makes an error, it will be crossed through with a single line in such a way to ensure that the original entry can still be read. The correct entry will then be clearly inserted. The amendment will be initialled and dated by the person making the correction immediately. Overwriting or use of correction fluid will not be permitted.

It is the Investigator's responsibility to ensure the accuracy of all data entered and recorded in the CRFs. The Delegation of Responsibilities Log will identify all study personnel responsible for data collection, entry, handling and managing the database.

There is no requirement for access to medical records. All study data will be entered directly onto CRFs either directly by the participant or by the study investigator.

The following standard tools will be executed directly into the CRF:

- Edinburgh Handedness Inventory
- Karolinska scale
- Depression Anxiety, Stress score
- Client Satisfaction Questionnaire (CSQ-8)
- CyberSickness in Virtual Reality Questionnaire (CSQ-VR)
- NASA – Task Load Index scale
- Witmer and Singer Presence Questionnaire.

The following tools are conducted on an online platform (a unique study identifier will be used if required) and their results inputted into the CRF:

- Psychomotor Vigilance test score
- Anti-Saccade test
- Mental Rotation Task
- Visual Search Task using Divided Attention
- Cognitive Demand Battery (CBD)
- Anatomical knowledge test score.

13.3 DATA HANDLING AND ANALYSIS

We will use RStudio to analyse data with appropriate packages.
Examples include: Library (here, janitor, tidyverse, psych, dplyr, Hmisc, finalfit, ltm, lme4).
Data will be stored on a University of Dundee managed laptop and OneDrive UoD database. Professor McLeod will be responsible for data analysis and storage. He will provide a report using Quatro.

13.4 ARCHIVING ARRANGEMENTS

The study documents (including the Trial Master File (TMF), Case Report Forms (CRFs), Informed Consent Forms (ICFs) along with the study database) will be kept for a minimum of five years. They will be stored in locked offices within the Royal National Orthopaedic Hospital NHS Trust (RNOH). The CI is responsible for the secure archiving of study documents. The study database will also be kept electronically on the RNOH computer network, for a minimum of five years.

The study documentation will be prepared for archiving by the CI/PI or research team in line with the RIC Archiving SOP.

Site PI's will be responsible for archiving all essential study documents for the study, in accordance with local R&D SOPs.

14. STATISTICAL DESIGN

14.1 SAMPLE SIZE AND RECRUITMENT

The study will be a cross-over equivalence study with 2 to 4 week washout period. We will use q-q plots to visualise the distribution of the data. If not, data will be transformed (*i.e.* log converted).
The primary outcome will be the Anatomical Knowledge score out of 44. Using PASS v24.0.2 (NCSS, Utah,) a two-sample, one-sided t-test for equivalence assuming equal variance, SD = 12, Power = 0.90, alpha = 0.05, difference between means = 6 and equivalence limits ± 6 points requires 102 participants. Therefore, we will aim to recruit 120 participants and allow for withdrawal of up to 15% of participants.
This will require recruitment of up to 30 participants per centre and require 2 visits to each centre. We anticipate this will take 6-12 months.

14.2 ENDPOINTS

14.2.1 Primary endpoints

Answers to individual questions I the Anatomical Knowledge test are pass/fail, giving a total range of possible scores between 0 and 44 for the assessment. Data will be analysed using a two-sample, one-sided t-test for equivalence and expressed as mean and differences with 90% confidence intervals.

14.2.2 Secondary endpoints

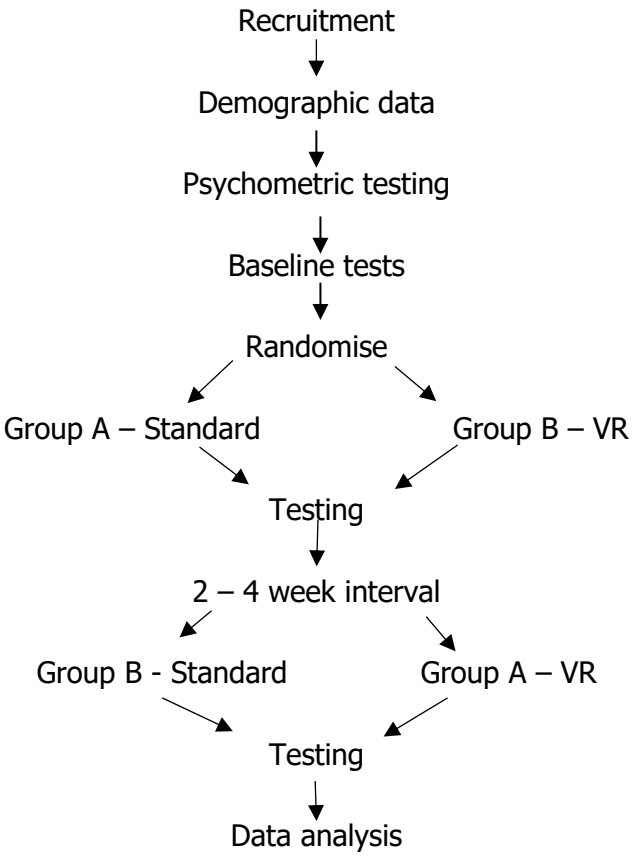
- Handedness (Edinburgh Handedness Inventory) expressed as % of left or right handedeness
- Subjective sleepiness (Karolinska scale). Eight point scale from extremely alert to extremely sleepy
- Motor reaction time (Psychomotor Vigilance test) – measures response time in milliseconds[6]
- Attention control (Anti-Saccade test) – a test of inhibitory control by tracking eye movements away from or towards targets in milliseconds)[7]
- Mental rotation (Mental Rotation Task) – Correct proportion of responses and time taken in milliseconds[8]
- Depression Anxiety, Stress (DASS score)
- Visual Search Task (Divided Attention) - Correct proportion of responses and time taken in milliseconds[9]

10.3 TREATMENT PROCEDURE

After training and testing

- Acceptability: Client Satisfaction Questionnaire (CSQ-8) – Eight questions assessed using 4-point categorical scale from poor to excellent[10]
- Usability: CyberSickness in Virtual Reality Questionnaire (CSQ-VR)[11]
- Immersion: Witmer and Singer Presence Questionnaire[12]
- Subjective workload (NASA – TLX scale) – Six items judged on 21-point scale[13]
- Cognitive Demand Battery (CBD) – Target difference and duration in milliseconds[14]
- Resource use: Calculation of cost differences between learning modalities

14.3 STATISTICAL ANALYSIS PLAN



14.3.1 Primary endpoint analysis

Answers will be pass/fail, giving a range of scores between 0 and 44 for the knowledge test. Data will be analysed using a two-sample, one-sided t-test for equivalence and expressed as mean and differences with 90% confidence intervals. The primary outcome will be the score out of 44. Using PASS v24.0.2 (NCSS, Utah,) a two-sample, one-sided t-test for equivalence assuming equal variance, SD = 12, Power = 0.90, alpha = 0.05, difference between means = 6 and equivalence limits ± 6 points requires 102 participants. Therefore, we will aim to recruit 120 participants and allow for withdrawal of up to 15% of participants.
This will require recruitment of up to 30 participants per centre and require 8 visits to each centre. We anticipate this will take 4 months.

14.3.2 Secondary endpoint analysis

Secondary analyses will be performed based on the type of data and their distribution. Comparison of groups will use parametric or non parametric tests as appropriate.

14.4 RANDOMISATION

Randomised cross over design for equivalence.

14.5 INTERIM ANALYSIS (IF APPLICABLE)

Not applicable

14.6 OTHER STATISTICAL CONSIDERATIONS

Not applicable

15. COMMITTEES INVOLVED IN THE STUDY

1. **Trial Management Group (TMG)** – This will consist of the study investigators and be chaired by the Chief Investigator (CI). The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. It will meet (using online platform) at least once per month during the study but it is anticipated that the TMG will conduct ad hoc meetings and correspondence *via* email on a more regular basis to ensure study proceeds on time.

16. MONITORING AND AUDITING

The requirement for study monitoring or audit will be based on the internal RNOH RIC risk assessment procedure and applicable Standard Operating Procedures (SOPs). It is the responsibility of the RIC to determine the monitoring risk assessment and explain the rationale to the study research team.

Study monitoring and/or audit will be discussed with the CI before arrangements are made to conduct the visit.

17. DIRECT ACCESS TO SOURCE DATA

The Investigator(s)/institution(s) will permit study-related monitoring, audits, REC review, and regulatory inspection(s), providing direct access to source data/documents. Study participants are informed of this during the informed consent discussion.

18. ETHICS AND REGULATORY REQUIREMENTS

The Sponsor will ensure that the study protocol, Participant Information Sheet (PIS), Informed Consent Form (ICF) are submitted supporting documents have been approved by the Health Research Authority (HRA) which includes Research Ethics Committee (REC) approval if applicable, prior to any participant recruitment taking place. The protocol and all agreed substantial protocol amendments, will be documented and submitted for HRA approval prior to implementation.

Before site(s) can enrol participants into the study confirmation of capacity and capability must be issued by the institution hosting the trial (unless HRA specifically has confirmed in the HRA approval letter that this is not required). It is the responsibility of the PI at each site to ensure that all subsequent amendments gain the necessary approvals by the participating site. This does not affect the individual clinician's responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

Within 90 days after the end of the study, the CI will ensure that the REC is notified that the study has finished. If the study is terminated prematurely, those reports will be made within 15 days after the end of the study.

The CI will supply a final summary report of the clinical study to the REC and the Sponsor in parallel within one year after the end of the study.

19. FINANCE

This study is funded by the National Institute of Academic Anaesthesia and Regional Anaesthesia UK Society grant.

20. INSURANCE AND INDEMNITY

NHS bodies are liable for clinical negligence and other negligent harm to individuals covered by their duty of care. NHS Institutions employing researchers are liable for negligent harm caused by the design of studies they initiate.

21. PUBLICATION POLICY

Data ownership rights will lie with the institution sponsoring the study.

22. STATEMENT OF COMPLIANCE

The trial will be conducted in compliance with the protocol, Sponsor's Standard Operating Procedures (SOPs), GCP and the applicable regulatory requirement(s).

The study conduct shall comply with all relevant laws of the UK country in which the study site is located including but not limited to, the Human Rights Act 1998, the Data Protection Act 2018,

and with all relevant guidance relating to medicines and clinical studies from time to time in force including, but not limited to, the ICH GCP**,** the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (2008 Version), the UK Policy Framework for Health and Social Care Research.

This study will be conducted in compliance with the protocol approved by HRA and according to RGF standards. No deviation from the protocol will be implemented without the prior review and approval of the Sponsor and HRA, except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the Sponsor and the REC as soon as possible.

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24. LIST OF PROTOCOL APPENDICES

Appendix 1 *Study Assessments*

Handedness (Edinburgh Handedness Inventory)

Edinburgh Handedness Inventory

Surname_____Given Name_____

Date of Birth_____Sex_____

Please indicate your preferences in the use of hands in the following activities by *putting + in the appropriate column*. Where the preference is so strong that you would never try to use the other hand unless absolutely forces to, *put* ++. If any case you are really indifferent put + in both columns.

Some of the activities require both hands. In these cases the part of the task, or object, for which hand preference is wanted is indicated in brackets.

Please try to answer all the questions, and only leave a blank if you have no experience at all of the object or task.

	Left	Right
1. Writing		
2. Drawing		
3. Throwing		
4. Scissors		
5. Toothbrush		
6. Knife (without fork)		
7. Spoon		
8. Broom (upper hand)		
9. Striking Match (match)		
10. Opening box (lid)		
i. Which foot do you prefer to kick with?		
ii. Which eye do you use when using only one?		

L.Q.	Leave the spaces blank	DECLE

Subjective sleepiness (Karolinska scale)

KAROLINSKA SLEEPINESS SCALE

Please, indicate your sleepiness during the five minutes before this rating through circling the appropriate description

1=extremely alert
2=very alert
3=alert
4=rather alert
5=neither alert nor sleepy
6=some signs of sleepiness
7=sleepy, but no effort to keep awake
8=sleepy, some effort to keep awake
9=very sleepy, great effort to keep awake, fighting sleep

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Original study: Åkerstedt, T. and Gillberg, M. Subjective and objective sleepiness in the active individual. *International Journal of Neuroscience*, 1990, 52: 29-37.

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Motor reaction time (Psychomotor Vigilance test)
Psychomotor Vigilance Test - Millisecond
Attention control (Anti-Saccade test)
AntiSaccade Task - Millisecond
Mental rotation (Mental Rotation Task)
Mental Rotation - Millisecond
Depression Anxiety, Stress (DASS score)
Depression Anxiety and Stress Scale (DASS) - Millisecond
Visual Search Task (Divided Attention)
Visual Search Task - Millisecond
Knowledge pre-training
https://www.classmarker.com/online-test/start/?quiz=qkv65b26f703fd6d (Sample question)
Acceptability: Client Satisfaction Questionnaire (CSQ-8)
CSQ Versions – CSQScales
Usability: CyberSickness in Virtual Reality Questionnaire (CSQ-VR)
OSF | CSQ-VR_CybersicknessVRQuestionnaire111 (1).pdf
Immersion: Witmer and Singer Presence Questionnaire
PRESENCE QUESTIONNAIRE (wordpress.com)
Subjective workload (NASA – TLX scale)
NASA Task Load Index (NASATLX) - Millisecond
Cognitive Demand Battery (CBD)
Cognitive Demand Battery (CDB) - Millisecond

Inquisit software
Millisecond

Sample regional anaesthesia workshop videos
Erector Spinae Plane Block - YouTube

Appendix 1

Summary chart of study Assessments (Template)

Please see Section 10.3 of the study protocol.

Appendix 2

Summary of Amendment History (Template)

List details of all protocol amendments here whenever a new version of the protocol is produced.
All study amendments must be submitted to the Sponsor for approval prior to submission to the REC/HRA.

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made