ConsCIOUS-3:

Noradrenergic Suppression to Reduce Connected Consciousness After Intubation- A Randomised, Placebo-Controlled Trial

Protocol Number:	X21-0410
Principal Investigator: **Associate Investigators:**	Professor Robert Sanders Dr. Tim McCulloch Dr. Gerald Wong Dr. John Loadsman Dr. Jessica Lim Tom Payne Justin Wu Kaitlin Kramer
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Protocol Version:	Version 1.4
Protocol Date:	17.05.2022

Principal Investigator:

Professor Robert Sanders

Signature:_____ Date:_____

Ethics Statement:

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

Protocol Version	**Date**	**Amendments**
1.1	**10.11.2021**	**Updated to reflect changes with initial Ethics query**
1.2	**15.11.2021**	**Removed bio specimen collection details**
1.3	**16.02.2022**	**Visual Analogue Scale for pain changed to pain score** **Removed Post-intubation commands a,b,c from CRF (appendix 1)** **Added associate investigators**
1.4	**09/05/2022**	**Removed video recording from study procedure** **Glycopyrrolate administration after study drug** **Added Justin Wu (associate investigator)** **CRF altered to reflect sequential data collection**

Glossary of Terms

ASA	**American Society of Anaesthesiology Physical Status Classification System**
ATN	**Attention Network Test**
BIS	**Bispectal Index**
CRF	**Case Record File**
3D CAM	**Cognitive Assessment Method**
DRS-R-98	**Delirium Rating Scale- Revised-98**
DSMB	**Data Safety and Monitoring Board**
EEG	**Electroencephalogram**
IFT	**Isolated Forearm Technique**
POD	**Post Operative Day**
RASS	**Richmond Agitation and Sedation Scale**
RCT	**Randomised Control Trial**
SWA	**Slow Wave Activity**
TICS-M	**Telephone Interview of Cognitive Status**

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Summary

Study title:	ConsCIOUS-3: Noradrenergic Suppression to Reduce Connected Consciousness after Intubation- A randomised, placebo-controlled trial
Protocol version:	Version 1.4 , Dated 09.05.2022
Objectives	
Primary objective:	Pilot study of whether adjunct dexmedetomidine may reduce rises in the Bispectral Index (BIS) following intubation
Secondary Objectives:	**1)** Pilot study of whether dexmedetomidine may reduce isolated forearm technique responsiveness after intubation
	2) Confirm the safety of adjunct dexmedetomidine for intubation
	3) To pilot whether adjunct dexmedetomidine may reduce BIS arousal in females
	4) Investigate influence of stage of menstrual cycle, anaesthetic dosing and response to intubation
	5) To test whether adjunct dexmedetomidine may reduce intraoperative awareness
	6) Influence of adjunct dexmedetomidine on post-operative pain scores
	6) Whether adjunct dexmedetomidine may reduce instance and severity of post-operative delirium
Study design:	Randomized Controlled Trial, sex-based stratified randomisation
Planned sample size:	52 subjects
Selection criteria:	Healthy (ASA 1, 2 or 3) subjects undergoing intubation for general anaesthesia
Study procedure:	Single Site, randomized control trial, trial drug (dexmedetomidine) or placebo given during general anaesthetic induction.
Statistical considerations:	Sample size calculation Yes
	Analysis plan Yes
Duration of Study:	1 year

1. BACKGROUND AND INTRODUCTION

1.1. DISEASE/PROPOSED INTERVENTION BACKGROUND

Anaesthesia is proposed to be a state of unawareness, and explicit memory of intraoperative events is rare (0.1-0.2%)[1-4]. However, intraoperative awareness, without explicit recall, may occur in at least 5% of subjects[5,6]. While a 5% intraoperative awareness rate is several orders of magnitude higher than the incidence of explicit memory under anaesthesia, a subgroup analysis of first study suggested the rates may be up to 12% in patients under 40 years old[5]. Hence, we conducted ConsCIOUS2, focussed on young adults (18-40 years old), who are typically considered high risk for awareness, and identified that 11% of young adults showed evidence of intraoperative awareness. Importantly, females were more likely to respond than males ($OR_{adjusted}$ = 2.7, 95% CI [1.1, 7.4], p=0.024), behoving us to identify ways in which to address this issue.

Our recent survey of the public identified that 60% of participants felt it was unacceptable to be aware of intraoperative events even if they could not recall them afterwards[7]. Further, implicit memory and intraoperative awareness have been associated with reduced postoperative satisfaction, dysphoria and post-traumatic stress disorder[3,5,8].

In order to assess intraoperative awareness in a way that is not dependent on memory, we employed the isolated forearm technique[9]. A sphygmomanometer cuff is inflated on the forearm to isolate the hand from the circulation, preventing it being paralysed during neuromuscular blockade. Subjects are then asked to squeeze a researcher's hand to signify a volitional response to command, which in humans is the gold-standard definition of consciousness.

1.2. RATIONALE FOR PERFORMING THE STUDY

Given the known role of noradrenaline in (1) the fight or flight response, (2) awareness to external stimuli, including through salience-driven attention mediated by the ventral attention network, and (3) the relative lack of suppression of the locus coeruleus by propofol and volatile anaesthetic agents, we have hypothesized that additional noradrenergic suppression may be required to reduce the incidence of intraoperative awareness[6]. Furthermore, there is some data suggesting that this may be particularly advantageous for females[10]. The dose of anaesthetics required to induce loss of consciousness varies by stage of menstrual cycle and so, as a secondary endpoint in females, we will assess how menstrual cycle affects the endpoints in this study[25]. Herein, we will conduct a pilot randomized controlled trial to provide preliminary data to support a larger study to refine induction techniques in anaesthesia for young people. This pilot study is powered to focus on EEG arousal and in the future we plan to power investigations for intraoperative awareness.

Dexmedetomidine, Propofol and Induction of anaesthesia

Propofol is the most utilised induction agent in anaesthesia worldwide. However, it is often coupled with an analgesic, as it does not have any analgesic properties in and of itself. Controlling the intense stimulus of intubation is important as it can cause a hypertensive crisis and awareness if not managed appropriately. The alpha2 adrenoceptor agonist dexmedetomidine has been compared against propofol for the induction of anaesthesia and interestingly dexmedetomidine was better at maintaining haemodynamic stability than propofol[11]. Dexmedetomidine usually however cannot achieve complete anaesthesia on its own, however a combination with propofol could be a clinically useful combination. In particular dexmedetomidine has shown to be safe and efficacious as a premedicant, particularly in children, where its sedating and anxiolytic properties are particularly helpful.

Dexmedetomidine has been tested against endpoints designed to observe this. In a crossover design study, one group of patients was commenced on a dexmedetomidine infusion to achieve a steady plasma concentration of 0.66ng/ml. After this was achieved a propofol infusion was gradually increased and endpoints tested against a saline control group. These endpoints included concentration of propofol required to achieve loss of ability to hold a syringe, loss of eyelash reflex, and loss of motor control to electrical stimulation. The amount of propofol required to achieve these endpoints was shown to be just over half the requirement in the test group vs the control group, demonstrating an advantageous pharmacodynamic interaction between the two drugs[12].

Our main interest of enquiry is the usefulness of dexmedetomidine during intubation and there have been a number of studies which demonstrate the effects of this. The usual loading dose of dexmedetomidine used to study this effect is 1microg/kg as a bolus, along with propofol to achieve loss of consciousness. All of these studies show a significant reduction in haemodynamic response to intubation when dexmedetomidine is utilised during intubation as compared to saline placebo[13,14,15,16,17,18]. These studies measured changes in blood pressure and heart rate, insinuating that dexmedetomidine attenuates the haemodynamic response via attenuation of catecholamine release, however this has not specifically been measured directly via blood sampling. In a direct comparison with the beta blocker labetalol, dexmedetomidine was also considered superior in achieving haemodynamic stability with fewer adverse side effects[14].

Whilst most studies utilise a 1mcg/kg loading dose of dexmedetomidine, it does appear that even a 0.5mcg/kg loading dose is significantly effective, whilst reducing the unwanted side effects of dexmedetomidine such as bradycardia and hypotension. A randomised double blind placebo controlled study compared the effects of a 0.5microg/kg loading dose and a 1microg/kg loading dose of dexmedetomidine, and compared both to a saline control. Both loading doses showed equal effectiveness in reducing propofol dose required for induction, and blunting the haemodynamic response to laryngoscopy and intubation. The lower dose was associated with less hypotension and bradycardia[19].

In addition, a 2015 study utilised 0.5microg/kg loading of dexmedetomidine and demonstrated that the mean total dose of propofol required for induction was almost half of that in the control group. It also showed an approximate 33% reduction in systolic blood

pressure rise, an approximate 40% reduction in diastolic blood pressure rise, and approximately 35% reduction in mean blood pressure rise[20].

It should be noted that the bispectral index (BIS) depth of anaesthesia monitor can monitor loss of consciousness when dexmedetomidine is utilised in addition to propofol as compared to propofol alone or in combination with an opioid[21,22].

It is worth stressing that dexmedetomidine has shown to be safe and efficacious as a premedicant, particularly in children, where its sedating and anxiolytic properties are particularly helpful[24] and hence in this context dexmedetomidine can be considered in line with standard of care.

2. HYPOTHESIS

We hypothesize that dexmedetomidine will reduce the rise in "brain activity" detected by the Bispectral Index (BIS) monitor following intubation.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVES

1. To determine if adjunct dexmedetomidine may reduce increases in the BIS following intubation

3.2. SECONDARY OBJECTIVES

1. Pilot study of whether dexmedetomidine may reduce isolated forearm technique responsiveness after intubation
2. To confirm the safety of adjunct dexmedetomidine for intubation
3. To pilot whether dexmedetomidine is particularly useful in females in reducing BIS arousal
4. Investigate the influence of stage of menstrual cycle on anaesthetic dosing and response to intubation
5. To test whether adjunct dexmedetomidine reduces the incidence of recalled intraoperative awareness as assessed by the Brice Questionnaire
6. Post-operative pain score
7. Instance and severity of post-operative delirium

8. Incidence and severity of postoperative nausea and vomiting

4. STUDY DESIGN

4.1. DESIGN

The study is a randomised (saline) controlled trial of 52 participants with sex-stratified randomization.

4.2. EXPECTED PARTICIPANT NUMBERS

N=52

4.3. DURATION OF THE STUDY

1 Year of Recruitment at RPAH.

4.4. ENDPOINTS

PRIMARY ENDPOINTS

Rise in BIS values from pre-intubation to post-intubation

SECONDARY ENDPOINTS

1. Responsiveness on the IFT post-intubation between groups
2. Changes in perioperative blood pressure and heart rate
3. Sex-based differences in BIS, IFT and haemodynamic responsiveness to dexmedetomidine
4. The frontal EEG characteristics of responsiveness or not on the IFT
5. The association of stage of menstrual cycle with dose of anaesthetics required for loss of consciousness or BIS rise following intubation or responsiveness on IFT
6. Incidence and severity of postoperative nausea and vomiting
7. Postoperative pain score
8. Instance and severity of post-operative delirium in recovery

4.5 CENTRES

Royal Prince Alfred Hospital

5. STUDY PARTICIPANTS

5.1. INCLUSION CRITERIA

Adults requiring intubation for general anaesthesia

Sex: Females and Males

Age range: 18-40 years old

Willingness to Provide informed consent and participate and comply with study requirements

Healthy (ASA status 1, 2 or 3)

EXCLUSION CRITERIA
Women lactating, or pregnant.

Participants with a history of allergy to dexmedetomidine or history of heart block.

Participants who may have received an investigational new drug within the last 7 days

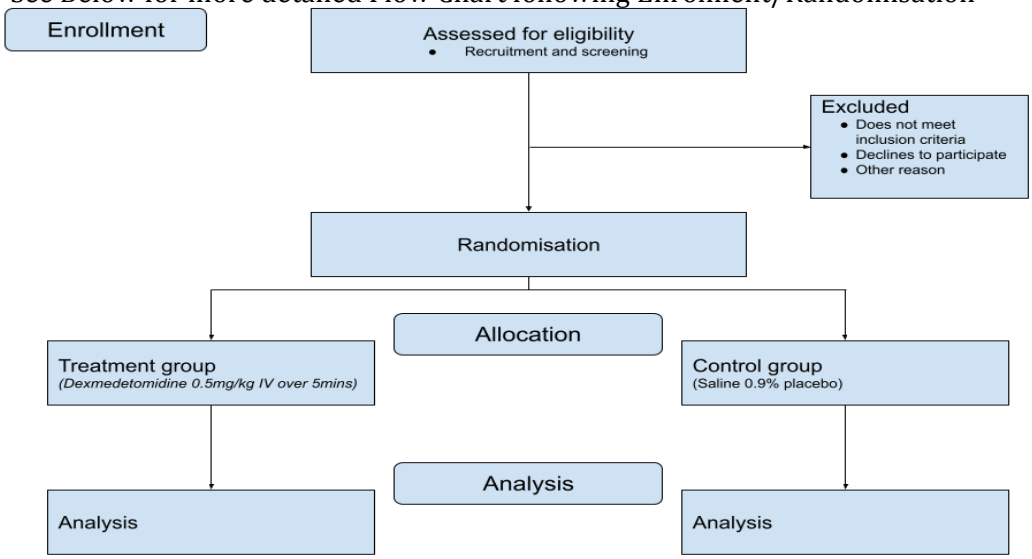
Participants with a history of a psychological illness or other conditions which may interfere with their ability to understand the study requirements.

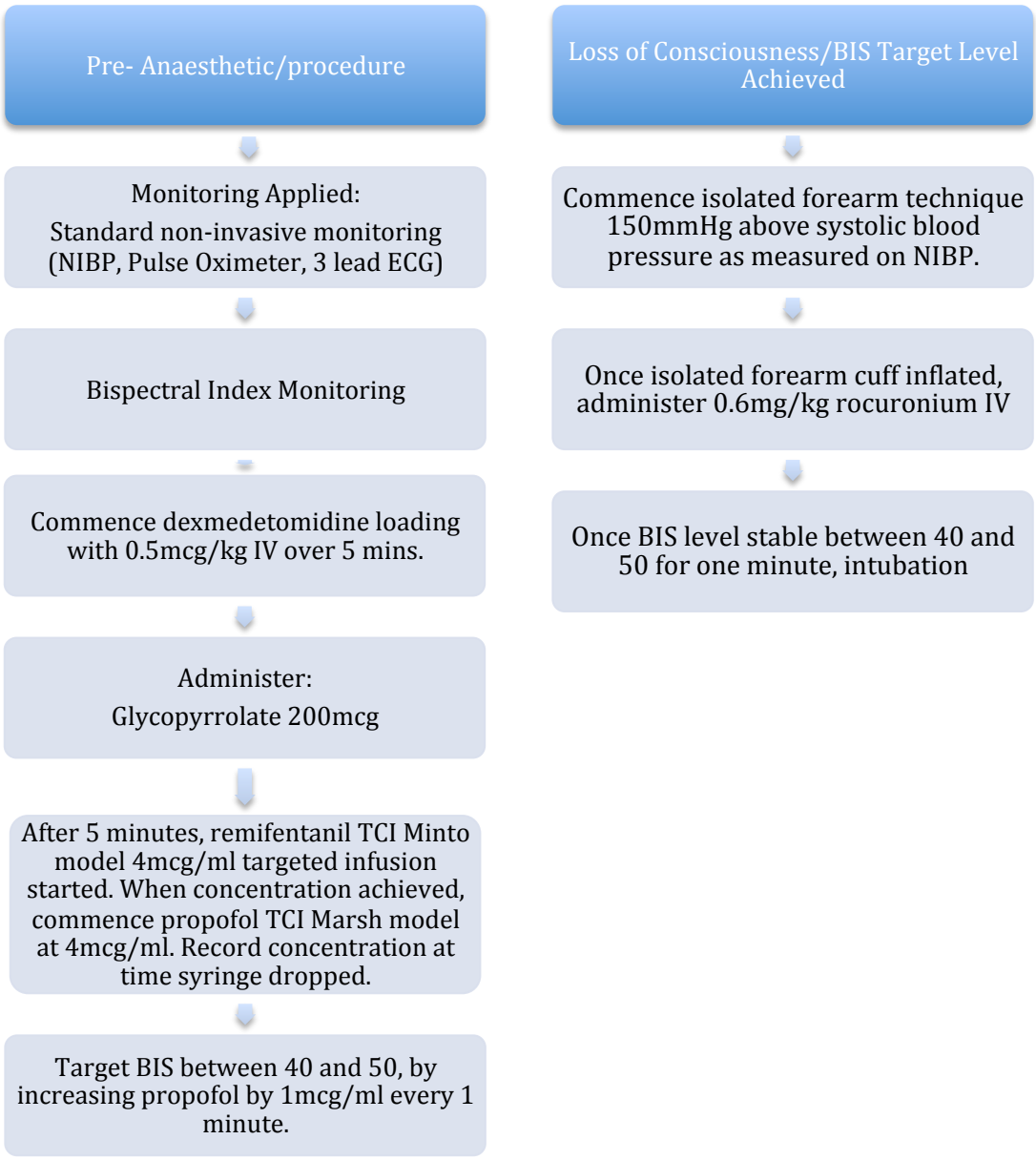
Participants with cognitive impairment that is likely to interfere with the evaluation of the participant's safety and of the study outcome.

6. STUDY PROCEDURES

6.1. STUDY FLOW CHART

See Below for more detailed Flow Chart following Enrolment/Randomisation




Pre- Anaesthetic/procedure
Monitoring Applied:
Standard non-invasive monitoring (NIBP, Pulse Oximeter, 3 lead ECG)
Bispectral Index Monitoring
Commence dexmedetomidine loading with 0.5mcg/kg IV over 5 mins.
Administer:
Glycopyrrolate 200mcg
After 5 minutes, remifentanil TCI Minto model 4mcg/ml targeted infusion started. When concentration achieved, commence propofol TCI Marsh model at 4mcg/ml. Record concentration at time syringe dropped.
Target BIS between 40 and 50, by increasing propofol by 1mcg/ml every 1 minute.
Loss of Consciousness/BIS Target Level Achieved
Commence isolated forearm technique 150mmHg above systolic blood pressure as measured on NIBP.
Once isolated forearm cuff inflated, administer 0.6mg/kg rocuronium IV
Once BIS level stable between 40 and 50 for one minute, intubation

Measurements:

NIBP minutely

Heart rate minutely

BIS value

Pre-dexmedetomidine baseline

Post dexmedetomidine at 1, 3 and 5 mins (Pre-induction)

Post induction every 2 minutes.

Post intubation at 1, 2, and 5 mins

Dose of propofol for loss of consciousness (syringe drop)

Positive or negative physical response (defined as IFT responsiveness within 1 min of intubation)

24 hours post operative, patient interviewed and asked if any awareness of events during induction of anaesthesia.

Frontal EEG differences between dexmedetomidine and placebo

6.2. INVESTIGATION PLAN

Methodology

Interventions	Enrolment Visit	Visit 1 Intraoperative Care	Visit 2 (PACU 15 min and 60 min)	Visit 3 Postoperative visit 24 hours	Visit 4 Postoperative visit 7 days
Participant Consent	X				
Inclusion/ Exclusion Criteria	X				
Pre-Operative Questionnaire (Females)	X				
Randomisation & drug treatment		X			
BIS/EEG and IFT data		X			
Anxiety/Pain/ PONV Score			X		
Delirium Assessments*			X		
Brice and satisfaction questionnaire				X	X
Adverse Event & Serious Adverse Event Assessment		X		X	

All intra-operative procedures including the administration of dexmedetomidine follow standard practice within general anaesthesia.

*As per the Case Record File (appendix 1) the post-operative delirium assessments will be conducted in recovery at 15 minutes post-operation and 60 minutes post-operation. The assessments will include the Richmond Agitation and Sedation Scale (RASS), Confusion Assessment Method ICU (CAM-ICU) and Nursing Delirium Screening Scale (NuDESC).

6.3. STUDY PROCEDURE RISKS

Dexmedetomidine is an approved sedative and can induce hypotension, bradycardia and complete heart block. This risk is increased when used in combination with other sedating agents. However, the risk of these events is most often seen in the elderly and patients with comorbidities (e.g. diabetes, chronic hypertension, severe cardiac disease). The risk of bradycardia will be offset by the addition of glycopyrrolate/atropine as a premedication and the population to be assessed will be young patients (18-40)). The expected haemodynamic effects of combining dexmedetomidine and propofol will also be offset by a likely overall dose reduction of propofol to achieve the desired BIS. On balance the approach of combining dexmedetomidine and propofol should not increase risk, consistent with prior publications[19,20].

6.4. PARTICIPANT RECRUITMENT AND SCREENING

Participants will be screened using the surgical lists and their date of birth to ensure they meet basic eligibility criteria. Their medical history and ASA status will also briefly reviewed by a member of the research team (within the department of anaesthetics) or by anaesthetic doctor to ensure they are ASA 1-3 and have no serious medical issues.

The anaesthetic team assessing the patient in the pre-admission clinic will ask the patient if they are willing to be contacted in regard to participation in research activities, following this the anaesthetic doctor will introduce the research team member or the research team member will contact the participant. The participant will be approached in the pre-admission clinic or over the telephone prior to the day of surgery, during this call they will be provided with information on the trial in both verbal and written form. They will be given sufficient time to discuss their involvement with their family and ask questions.

During the screening and recruitment process the treating surgical team will be contacted to ensure their support for the participant to be involved in the research project.

Will participants be screened?	Yes
If yes, what data will be collected? (NB, if participant is not eligible, will data collected be destroyed or kept?) This should be mentioned in PIS/CF)	Patients will be screened via the theatre lists to determine eligibility based on type of procedure and age. ASA status will be determined for eligibility at this time. Screening logs will not be collected.
Who will make initial contact with participants?	The initial contact with the patient will be made by a member of the anaesthetic department in the pre-admission clinic. Following this the anaesthetic doctor or a member of the research team will contact the patient to discuss involvement in the trial.

Who will perform the consent process? How will this be carried out?	Prior to obtaining consent the research team member will ensure the participant is capable of providing legal consent – based on their literacy, ability to understand the study and ensuring they are not influenced by power dynamics. Informed consent will be obtained prior to surgery by a member of the research team. eConsent will be obtained using RedCap if feasible. Paper copies will be kept in the participants medical records, a copy will be given to the participant and one will be stored in a locked file within the department of anaesthetics.
Will participants be consented verbally/explicitly/using eConsent?	eConsent will be used when feasible, alternatively paper based consent forms will be used as noted above.
Will participants be given a specific time period to consider participating?	Yes, participants will be given time in between their visit to the pre-admission and their day of surgery to consider participating and before providing informed consent.
Review of existing databases or databanks (please identify the database/databank and the custodian)	RedCap will be used to obtain eConsent and collect/transcribe data collected during this study.
Review of clinic files (please include who will be reviewing these files, for example a research coordinator).	Clinic files will be reviewed by the Clinical Research Coordinator (Department of Anaesthetics) and the principal investigator.
Advertisements (please include where the advertisement will be placed for example, in a newspaper, poster in a clinic or hospital foyer, radio announcements, website etc.)	Currently there is no plan for advertising.
Information Letter to Medical practitioners	No, the treating surgical team will be informed during the recruitment and screening process to ensure they support their patient's involvement.
Explain how potential participants will be screened for the study	Participants will be screened via the surgical lists for JL theatres.
Any other potential recruitment methods.	N/A

6.5. PARTICIPANT ENROLMENT

Prior to participant enrolment the treating surgical team will be informed to ensure their support, given the nature of the study surgical involvement is not required during research activities. The anaesthetic doctor will communicate details of the study with the surgical team and inform them of the additional time required to complete the study during intubation. If any issues arise with patient involvement this will be discussed with the treating surgical team, anaesthetics and coordinating investigator.

Potential participants will be enrolled into the study after the informed consent process has been completed and the participant has been assessed to meet all the inclusion criteria and none of the exclusion criteria. Study participants will receive a study enrolment number and this will be documented in the participant's medical record and on all study documents.

During patient enrolment and consent female participants will be asked to complete a questionnaire on contraception and menstruation (see appendix).

6.6. INFORMATION AND CONSENT

Informed consent will be obtained from eligible patients prior to their procedure. Participants will be assessed for ability to given informed consent, their literacy/language abilities and risk of unequal power dynamics in patient/doctor relationships. A Patient Information Consent Form with their signature and signature of the study doctor or research coordinator will be copied and filed in their medical records and study file. Additionally, the patient will receive a copy of this document.

Where feasible electronic consent will be obtained using RedCAP.

6.7. RANDOMISATION PROCEDURE

The participant will be randomized by computer program (RedCap) into one of the interventional arms. At this visit the participant will be randomised to saline or dexmedetomidine and receive a Randomisation Number.

The coordinating principal investigator Robert Sanders or associate investigators will randomise the patient using RedCap. The details will be communicated to the treating anaesthetic doctor who will draw up and administer the study drug or placebo. During the anaesthetic the treating doctor (with guidance from Professor Robert Sanders or an associate investigator (anaesthetic doctor)) will perform the research activities. An associate investigator who is blinded to the study drug will observe and document the responses in the Case Report File (appendix 1). Patient follow up will be conducted by a blinded member of the study team/associate investigator in PACU and post-operatively at 24-hours and 7 days.

6.8. END OF STUDY TREATMENT/WITHDRAWAL PROCEDURE

The study will end at 7 days postoperatively.

6.9. PATIENT WITHDRAWAL

A patient may withdraw their consent at any time with no change to their surgical and post-surgical standard care.

7. OUTCOMES

7.1. Definition of Outcomes

1. Change in BIS value from pre-intubation to post-intubation
2. Responsiveness on the IFT post-intubation between groups
3. Changes in perioperative blood pressure and heart rate
4. The frontal EEG characteristics of responsiveness or not on the IFT (collected from the BIS monitor).

8. STATISTICAL CONSIDERATIONS

8.1. SAMPLE SIZE OR POWER CALCULATION

Power calculation:

Based on[23],50 subjects provides 90% power ($p<0.05$) to show a difference of 10 points in the BIS (SD = 11)[23]. We include 2 extra patients for loss to follow up. Total sample size is 52 participants.

8.2. PROVIDE A DETAILED ANALYSIS PLAN

1. Rise in BIS value from pre-intubation to post-intubation analysed by t-test (parametric) or Mann-Whitney (non-parametric)
2. Responsiveness on the IFT post-intubation between groups (Fischer's Exact test)
3. Changes in perioperative blood pressure and heart rate analysed by t-test (parametric) or Mann-Whitney (non-parametric)
4. The frontal EEG characteristics of responsiveness or not on the IFT (collected from the BIS monitor). We will calculate the power spectrum and then subdivide by power bands using matlab pwelch function. We will average the power for the 10s prior to intubation and test whether there are differences in power, analysed by t-test

(parametric) or Mann-Whitney (non-parametric). We will repeat this process for the 10s after intubation. Further analyses of the EEG may be then undertaken to identify differences in IFT responders or not.

9. DATA COLLECTION

9.1. PARTICIPANT REGISTRATION

Participants will be registered for the trial at the time of consent and will be provided with a study ID. On the day of surgery, the participant will be randomized by computer (via RedCap) to dexmedetomidine or placebo.

9.2. FORMS AND PROCEDURE FOR COLLECTING DATA

All data – including pre-operative assessment, intra-operative data and post-operative questionnaires will be collected on a paper Case Report File (see appendix) or recorded directly to an electronic CRF. Any paper CRFs will be de-identified and labelled with patient ID number and data will be transcribed to REDCAP database. All paper documents will be securely stored in a locked cabinet as per legal requirements. Paper documents will be destroyed 15 years post-study.

9.3. CASE REPORT FORMS AND SCHEDULE FOR COMPLETION

The Case Report Form will be provided in the appendix. The study is completed 7 days post-operation.

9.4. DATA FLOW

Protocol → CRF Design → Patient data collected in CRFs → Patient data in CRFs converted into raw data sets → Raw data sets → Create Tables/Listings/Figures → Create Analysis → Report

10. QUALITY CONTROL AND ASSURANCE

10.1. CONTROL OF DATA CONSISTENCY

All data will be collected by treating anaesthetic doctors (see CRF). Post-operative questionnaires will be provided to patients at 15 minutes post-operation, 24-hours post-operation and 7-days post-operation.

Data will be collected on paper CRFs and de-identified using patient id numbers. All data will be transcribed to REDCAP with permission to access only granted to study doctors and staff.

If feasible eCRFs will be used to ensure direct entry to improve efficiency and reduce entry errors, reduce data queries/missing data and maximise completed data.

10.2. PROTOCOL AMENDMENTS

All protocol amendments will be submitted to the HREC for approval prior to use. Trial centres will follow their local governance protocols to gain approval to commence this trial.

11. ETHICS

11.1. INVESTIGATOR AUTHORISATION PROCEDURE

Ethics and Governance approval will be obtained via the local HREC and governance offices prior to commencement of the study.

11.2. PATIENT PROTECTION

Research doctors and staff will ensure that the study is completed in accordance with the guidelines set out in the *National Statement on Ethical Conduct in Human Research* (2007) (the *National Statement*) and the *CPMP/ICH Note for Guidance on Good Clinical Practice* and any other relevant legislation/guidelines.

12. SAFETY

12.1. ADVERSE EVENT REPORTING

Adverse event

The Australian Clinical Trial Handbook (*The Handbook*) defines an adverse event (drugs) as:

> any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, symptom,

or disease temporally associated with the use of a medicinal (investigational/experimental) product, whether or not related to this product. [1]

Adverse drug reaction

The Handbook defines an adverse drug reaction as:

> For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered ADVERSE DRUG REACTIONS. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.
>
> For marketed medical products: a response to a drug which is noxious and unintended and which occurs normally used in man for prophylaxis, diagnosis or therapy of diseases of for modification of physical function.[2]

Serious adverse event (SAE) or Serious Adverse Drug Reaction is defined as:

> Any untoward medical occurrence that at any dose:
>
> - results in death;
> - is life-threatening, (NOTE: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event/reaction which hypothetically might have caused death if it were more severe)
> - requires in-patient hospitalisation or prolongation of existing hospitalisation;
> - results in persistent or significant disability/incapacity;
> - is a congenital anomaly/birth defect; or
> - is a medically important event or reaction.[3]

The specific adverse events that will be monitored during this research project will be:

- Adverse reactions to dexmedetomidine – including allergic reactions
- Signs of Distress during the procedure: Arousal (Pupils, Sweating, Tachycardic, Hypertension, Change in Depth of Anesthesia monitor

1
2
3

- Patient reported post-operative issues (as outlined in the satisfaction questionnaire – Case Report File- appendix 1)

Any adverse events deemed significant by the treating anaesthetic doctor will be noted in the Case Record File, reported to the study and transcribed to the RedCap Database.

Any adverse events or serious adverse events that compromises the ethical acceptability of the protocol will be reported to the local governance office as per policy.

12.2. SERIOUS ADVERSE EVENT REPORTING

All serious adverse events will be reported immediately to the sponsor and the HREC. The reports should be followed by a detailed written report. Follow-up reports should identify the participant/s by unique code assigned to participants (rather than by name).

12.3. DATA SAFETY AND MONITORING BOARD (DSMB)

Monitoring will be performed in accordance with GCP Monitoring guidelines and will be overseen by the DSMB which will include the following persons:

Prof Aeyal Raz (Israel)

Prof Jamie Sleigh (New Zealand)

Dr Amy Gaskell (New Zealand)

The study site may be subject to monitoring at discretion of the DSMB – which may include review of de-identified material, consent for this by patients will be included in the PICF. Additional audits may be deemed necessary by the appointed head of the DSMB.

The DSMB will meet at three monthly intervals to review the trial activities.

12.4. EARLY TERMINATION

If early termination of the research project is required, the Principal Investigator Professor Robert Sanders will communicate with the HREC and Governance offices. All policies and procedures will be followed and documented.

13. BLINDING AND UNBLINDING

Subjects will receive either a dexmedetomidine or saline infusion. The anaesthetists will not be blinded to drug allocation; research staff performing follow-ups will be blinded.

14. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY

Electronic data will be stored in a secured online database only accessible to those who are deemed to require access to the data for analysis purposes. Any staff who no longer require access to the online data will be removed from the database.

Paper CRFs will be kept in a locked secure file cabinet within the locked Department of Anaesthetics and keys will be kept in a safe location for those who require access. All documents will be held for 15 years as per legal requirements.

15. TRIAL FINANCING

Internal funding for this project will be provided through departmental resources

16. REFERENCES

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17. Appendices

Appenndix 1

Pre-operative Data	
DOB and AGE at enrolment	
Sex	M F
ASA Status	
Height (meters)	
Body Weight (kg)	
BMI	
Surgical Operation	
Comorbid Diseases and Conditions	
Chronic medications (dose, last time taken)	
Beta Blockers	Yes No

	Drug: Dose: Time:
Benzodiazepine before Intubation:	Yes No Drug: Dose: Time:
History of Anaesthesia Awareness	
Preoperative Anxiety Scale (1-10)	
Preoperative Pain Score (1-10)	

Pre-Procedure/Anaesthesia **Date of Procedure:** _____/_____/_____

Monitoring applied (standard non-invasive) ☐ Ensure 1 minutely recording for observations set on anaesthetic machine ☐ USB Key Inserted for EEG recording? (please tick when inserted) ☐		
Baseline EEG Date and Time: Eyes closed during baseline recording?	___/_____/_____ ; ____:____ Yes No	
Baseline BIS Value		
Administration of Glycopyrrolate and Study Drug		
Dexmedetomidine/Study Drug Loading Start: (0.5mcg/kg IV over 5 minutes- cont. to next step after 5 min)	Time _____:_____	
Peak BIS Value (in 1 minute post-dexmedetomidine)		Time _____:_____
BIS Value (at 3 minute post-dexmedetomidine)		Time _____:_____
BIS Value (at 5 minute post-dexmedetomidine)		Time _____:_____
Dexmedetomidine/Study Drug Finish:	Time _____:_____	
BIS Value (after administration of study drug)		

Administration of Glycopyrrolate 200mcg	Time _____:_____
Commence Remifentanil Infusion followed by Propofol Infusion	
BIS Value (at start of remifentanil)	
Commence remifentanil TCI (4mcg/mL- once concentration achieved cont. to next step)	Time _____:_____
BIS Value (at start of propofol)	
Commence propofol TCI (4ng/mL)	Time (commenced) _____:_____
Record time syringe dropped:	_____:_____
Remifentanil CE at drop	ng/ml
Propofol CE at drop	mcg/ml
BIS Value (at time of syringe drop)	
Target BIS between 40-50 by increasing propofol by 1mcg/ml every 1 minute	
BIS Value (prior to IFT)	
Commence IFT (150mmHg above systolic NIBP)	Time _____:_____
Administer 0.6mg/kg rocuronium IV (once cuff inflated)	Time _____:_____
Pre-intubation Commands (immediately prior to intubation)	
Tourniquet up time: _____:_____	Tourniquet down time:____:_____
TOF response? Y N	Time: _____:_____
1) 'X, squeeze my hand' Response (circle one):	Time: _____:_____ Definite Indeterminate None
2) 'X, if you are in pain squeeze my hand 2 times' Response (circle one)	Time: _____:_____ Definite Indeterminate None
3) 'X, if you are okay squeeze my hand 2 times' Response (circle one):	Time: _____:_____ Definite Indeterminate None
Signs of Distress/Arousal? (tachycardia, sweating, pupils, change in depth of anaesthesia, etc)	
BIS Value (post-IFT)	
Target BIS Between 40-50 for 1 minute, then intubate	

***BIS Value** (prior to intubation- as 02 mask removed)	
Remifentanil CE (prior to intubation- as 02 mask removed)	
Propofol CE (prior to intubation- as 02 mask removed)	
Intubation (start time): Time of Intubation (actual intubation):	Time _____:_____ Time _____:_____
Number of attempts (to intubate):	
Signs of spontaneous movement? Y N	Signs of distress?
Other drugs administered prior to intubation:	
Post-Intubation Commands	
BIS Value (10 sec post-intubation)	
Remifentanil CE (0-10 sec post-intubation)	ng/ml
Propofol CE (0-10 sec post- intubation)	Mmg/ml
Tourniquet up time: _____:_____	Tourniquet down time:____:_____
TOF response? Y N	Time: _____:_____
4) 'X, squeeze my hand' Response (circle one):	Time: _____:_____ Definite Indeterminate None
5) 'X, if you are in pain squeeze my hand 2 times' Response (circle one)	Time: _____:_____ Definite Indeterminate None
6) 'X, if you are okay squeeze my hand 2 times' Response (circle one):	Time: _____:_____ Definite Indeterminate None
Signs of Distress/Arousal? (tachycardia, sweating, pupils, change in depth of anaesthesia, etc)	
BIS Value (post-commands)	

***Peak BIS Value** (in 1 minute post-intubation)	Time _____:_____
Peak BIS Value (in 1-3 minute post-intubation)	Time _____:_____
Peak BIS Value (in 3-5 minute post-intubation)	Time _____:_____
Save BIS Data to USB and Remove USB Key ☐ **Print anaesthetic observations and collect from printer in PACU** ☐	
Emergence Data	
Procedure Finish:	Time: ____:____
Time of Extubation:	Time: _____:_____
Please return CRF to research staff or give to PACU staff to lock in cupboard. **Thank you.**	

Post-operative Data **Date of Assessment:**_____

15 minutes after arrival to PACU- Time: _____:_____

RASS Score	
Nu-DESC Score	
Anxiety Scale (1-10)	
Pain Score (1-10)	
PONV Score (0-none, 1- nausea, 2-vomiting)	

CAM-ICU 7

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

60 minutes after arrival to PACU- Time: _____:_____

RASS Score	
Nu-DESC Score	
Anxiety Scale (1-10)	
Pain Score (1-10)	
PONV Score (0-none, 1-nausea, 2-vomiting)	

CAM-ICU 7

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

Nu-DESC:

Time Period Symptom	15 minutes after admission into PACU	60 minutes after admission into PACU
I. Disorientation Verbal or behavioral manifestation of not being oriented to time or place or misperceiving persons in the environment • **Last name? Location? Year? Why here?**		
II. Inappropriate Behavior Behavior inappropriate to place and/or for the person; e.g. puling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like.		
III. Inappropriate Communication Communication inappropriate to place and/or for the person; e.g., incoherence, non-communicativeness, nonsensical or unintelligible speech.		
IV. Illusions/Hallucinations Seeing or hearing things that are not there; distortions of visual objects. • **In the last few minutes, have you seen or heard things that are not really there?** • **Is your vision or hearing distorted?**		

V. Psychomotor retardation Delayed responsiveness, few or no spontaneous actions/words; e.g., when the patient is prodded, reaction is deferred and/or the patient is unarousable.		
Total Score		

GUIDELINES TO SCORING:

DISORIENTATION:
0 = No signs of item present. Patient is orientated to time place and person.
1 = Mild to moderate, barely expressed and noticeable through to being present and undeniable. Patient still can provide some orientating information to time, place and/or person.
2 = Moderate to severe: patient is not orientated to time or place. I,e in severe impairment will be not able to tell you the date, month, day, year, season, floor, name of hospital, city, state, and country.

INAPPROPRIATE BEHAVIOUR:
0 = no signs of item present
1 = mild to moderate: Hyperactivity is barely noticeable or appears as simple restlessness, to undeniable, subject moves frequently.
2 = moderate to severe: Hyperactivity is severe; patient is constantly moving, overreacts to stimuli, requires surveillance and/or restraint

INAPPROPRIATE COMMUNICATION;
0 = no sign of items present: patient's speech is coherent and goal-directed
1 = mild to moderate: patient's speech is slightly difficult to follow; responses to questions are slightly off target, to disorganized speech being clearly present
2 = moderate to severe: conversation is impossible due to severely disorganized thinking or speech (e.g rambling, irrelevant, or incoherent speech, or by tangential, circumstantial, or faulty reasoning)

ILLUSIONS/HALLUCINATIONS:
0 = no sign of items present
1 = mild to moderate: misperceptions or illusions related to sleep, fleeting hallucinations
2 = moderate to severe: frequent or intense illusions or hallucinations that disrupts care, function or is associated with inappropriate behaviour.

PSYCHOMOTOR RETARDATION:
0 = no sign of items present
1 = mild to moderate: Hypoactivity is barely noticeable, expressed as slightly slowing of movement, to moderate slowing of movements.
2 = moderate to severe: Hypoactivity is severe; patient does not move or speak without prodding or is catatonic

24-Hour Post-operative Follow Up

Date of follow up: _____ *Time of follow up:* _____

At any stage after the operation, did you have the following (please check one box for each question 1-10):

	No	Yes, Moderate	Yes, Severe
1. Drowsiness	☐	☐	☐
2. Pain at the site of surgery	☐	☐	☐
3. Thirst	☐	☐	☐
4. Hoarseness	☐	☐	☐
5. Sore throat	☐	☐	☐
6. Nausea or vomiting	☐	☐	☐
7. Feeling cold	☐	☐	☐
8. Confusion or disorientation	☐	☐	☐
9. Pain at the site of the anesthetic injection	☐	☐	☐
10. Shivering	☐	☐	☐

	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied	N/A
11. How satisfied were you with the information you were given by the anesthetist before the operation?					
12. How satisfied were you waking up from anesthesia?					
13. How satisfied have you been with pain therapy after surgery?					
14. How satisfied were you with treatment of nausea and vomiting after the operation?					
15. How satisfied were you with the care provided by the department of anesthesia in general?					
16. Would you recommend this anesthetic service to friends and family?	☐ Yes ☐ No				

17. What is the last thing you remember before going to sleep (please check one box)?

☐	Being in the pre-operative area

☐	Seeing the operating room
☐	Being with family
☐	Hearing voices
☐	Feeling mask on face
☐	Smell of gas
☐	Burning or stinging in the IV line
☐	Other:

18. What is the first thing you remember after waking up (please check one box)?

☐	Hearing voices
☐	Feeling breathing tube
☐	Feeling mask on face
☐	Feeling pain
☐	Seeing the operating room
☐	Being in the recovery room
☐	Being with family
☐	Being in the intensive care unit
☐	Nothing
☐	Other:

19. Do you remember anything between going to sleep and waking up (please check <u>ALL</u> relevant boxes)?

☐	No
☐	Yes; Hearing voices
☐	Yes; being asked to squeeze the hand of the research staff
☐	Yes; Hearing events of the surgery
☐	Yes; being unable to move or breathe
☐	Yes; anxiety/stress
☐	Yes; feeling pain
☐	Yes; Sensation of breathing tube
☐	Yes; Feeling surgery without pain
☐	Yes; Other:

20. Did you dream during your procedure (please check one box)?

☐	No
☐	Yes; Please describe:

21. Were these dreams disturbing to you (please check box)?	☐ Yes ☐ No

22. What was the worst thing about your operation (please check one box)?

☐	Anxiety
☐	Pain
☐	Recovery Process
☐	Unable to carry out usual activities
☐	Awareness
☐	Other:

Thank you for taking the time to complete this questionnaire.

7-Day Post-operative Follow-Up

Date of follow up: _____ Time of follow up: ____:_____

At any stage after the operation, did you have the following (please check one box for each question 1-10):

	No	Yes, Moderate	Yes,Severe
1. Drowsiness	☐	☐	☐
2. Pain at the site of surgery	☐	☐	☐
3. Thirst	☐	☐	☐
4. Hoarseness	☐	☐	☐
5. Sore throat	☐	☐	☐

6. Nausea or vomiting	☐		☐		☐
7. Feeling cold	☐		☐		☐
8. Confusion or disorientation	☐		☐		☐
9. Pain at the site of the anesthetic injection	☐		☐		☐
10. Shivering	☐		☐		☐
	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied	N/A
11. How satisfied were you with the information you were given by the anesthetist before the operation?					
12. How satisfied were you waking up from anesthesia?					
13. How satisfied have you been with pain therapy after surgery?					
14. How satisfied were you with treatment of nausea and vomiting after the operation?					
15. How satisfied were you with the care provided by the department of anesthesia in general?					
16. Would you recommend this anesthetic service to friends and family?	☐ Yes ☐ No				

17. What is the last thing you remember before going to sleep (please check one box)?

☐	Being in the pre-operative area
☐	Seeing the operating room
☐	Being with family
☐	Hearing voices
☐	Feeling mask on face
☐	Smell of gas
☐	Burning or stinging in the IV line
☐	Other:

18. What is the first thing you remember after waking up (please check one box)?

☐	Hearing voices
☐	Feeling breathing tube
☐	Feeling mask on face
☐	Feeling pain
☐	Seeing the operating room
☐	Being in the recovery room

☐	Being with family
☐	Being in the intensive care unit
☐	Nothing
☐	Other:

19. Do you remember anything between going to sleep and waking up (please check <u>ALL</u> relevant boxes)?

☐	No
☐	Yes; Hearing voices
☐	Yes; being asked to squeeze the hand of the research staff
☐	Yes; Hearing events of the surgery
☐	Yes; being unable to move or breathe
☐	Yes; anxiety/stress
☐	Yes; feeling pain
☐	Yes; Sensation of breathing tube
☐	Yes; Feeling surgery without pain
☐	Yes; Other:

20. Did you dream during your procedure (please check one box)?

☐	No
☐	Yes; Please describe:

21. Were these dreams disturbing to you (please check box)?	☐ Yes	☐ No

22. What was the worst thing about your operation (please check one box)?

☐	Anxiety
☐	Pain
☐	Recovery Process
☐	Unable to carry out usual activities
☐	Awareness
☐	Other:

Thank you for taking the time to complete this questionnaire.

Pre-operative Questionnaire for Females

1. What is your current contraception if any?

[ ] None

[ ] Fertility awareness /withdrawal method

[ ] Condoms/cap/diaphragm

[ ] Combine oral contraceptive pill*

[ ] Progesterone only pill*

[ ] Contraceptive implant (implanon/Nexplanon)

[ ] Contraceptive intrauterine device (non hormonal)

[ ] Contraceptive intrauterine device (hormonal)

[ ] Sterilisation

*If you take a contraceptive pill have you missed any pills in the last week? Yes/No

2. Do you take any form of hormone therapy or replacement? Yes/No

Please specify medication:

3. Do you have regular periods? (please tick one box)
- Yes
- No, they have never been regular
- No, they have been irregular for a few months
- No, my periods have stopped

4. What is the usual interval between the start of one period and the start of your next period (cycle length)? _____days

5. How long do your periods usually last for? _____days

6. When was your last period? Please fill in the date of the first day of your last period (dd/mm/yy)

7. If you your periods have stopped, what best describes the reason you have not had a period in the last 12 months? (please tick one box)

- Menopause
- Currently pregnant
- Currently breast feeding
- Contraceptives e.g. hormonal IUD, contraceptive implants
- Medical e.g. medication, chemotherapy, radiotherapy
- Surgical e.g. uterus removed, ovaries removed, ablation (novasure)
- Other: please describe_____

Appendix 1: **Case ReCaseCad Case REcord File** **Pre-operative Data**	
DOB and AGE at enrolment	
Sex	M F
ASA Status	
Height (meters)	
Body Weight (kg)	
BMI	
Surgical Operation	
Comorbid Diseases and Conditions	
Chronic medications (dose, last time taken)	
Beta Blockers	Yes No Drug: Dose: Time:

Benzodiazepine before Intubation:	Yes No Drug: Dose: Time:
History of Anaesthesia Awareness	
Preoperative Anxiety Scale (1-10)	
Preoperative Pain Score (1-10)	

Pre-Procedure/Anaesthesia **Date of Procedure:** _____/_____/_____

Monitoring applied (standard non-invasive) ☐ USB Key Inserted for EEG recording? (please tick when inserted) ☐		
Baseline EEG Date and Time: Eyes closed during baseline recording?	____/_____/_____ ; _____:_____ Yes No	
Baseline BIS Value		
Administration of Glycopyrrolate and Study Drug		
Administration of Glycopyrrolate 200mcg	Time _____:_____	
Dexmedetomidine/Study Drug Loading Start: (0.5mcg/kg IV over 5 minutes- cont. to next step after 5 min)	Time _____:_____	
BIS Value (at 1 minute post-dexmedetomidine)		Time _____:_____
BIS Value (at 3 minute post-dexmedetomidine)		Time _____:_____
BIS Value (at 5 minute post-dexmedetomidine)		Time _____:_____
Dexmedetomidine/Study Drug Finish:	Time _____:_____	
BIS Value (after administration of study drug)		
Commence Remifentanil Infusion followed by Propofol Infusion		
BIS Value (at start of remifentanil)		
Commence remifentanil TCI (4mcg/mL- once concentration achieved cont. to next step)	Time _____:_____	
BIS Value (at start of propofol)		
Commence propofol TCI (4mcg/mL)	Time (commenced) _____:_____	
Record time syringe dropped:	_____:_____	
Remifentanil CE at drop	mcg	

Propofol CE at drop	mcg
BIS Value (at time of syringe drop)	
Target BIS between 40-50 by increasing propofol by 1mcg/ml every 1 minute	
BIS Value (prior to IFT)	
Commence IFT (150mmHg above systolic NIBP)	Time _____:_____
Administer 0.6mg/kg rocuronium IV (once cuff inflated)	Time _____:_____
Pre-intubation Commands (immediately prior to intubation)	
Tourniquet up time: ____:____	Tourniquet down time:___:____
TOF response? Y N	Time: ____:____
7) 'X, squeeze my hand' Response (circle one):	Time: ____:____ Definite Indeterminate None
8) 'X, if you are in pain squeeze my hand 2 times' Response (circle one)	Time: ____:____ Definite Indeterminate None
9) 'X, if you are okay squeeze my hand 2 times' Response (circle one):	Time: ____:____ Definite Indeterminate None
Signs of Distress/Arousal? (tachycardia, sweating, pupils, change in depth of anaesthesia, etc)	
BIS Value (post-IFT)	
Target BIS Between 40-50 for 1 minute, then intubate	
BIS Value (prior to intubation)	
Remifentanil CE (prior to intubation)	
Propofol CE (prior to intubation)	
Intubation (start time): Time of Intubation (actual intubation):	Time _____:_____ Time _____:_____
Number of attempts (to intubate):	
Signs of spontaneous movement? Y N	Signs of distress?
Other drugs administered prior to intubation:	

Post-Intubation Commands	
BIS Value (post-intubation)	
Remifentanil CE (post-intubation)	mcg
Propofol CE (post- intubation)	mcg
Tourniquet up time: _____:_____	Tourniquet down time:____:_____
TOF response? Y N	Time: _____:_____
10) 'X, squeeze my hand' Response (circle one):	Time: _____:_____ Definite Indeterminate None
11) 'X, if you are in pain squeeze my hand 2 times' Response (circle one)	Time: _____:_____ Definite Indeterminate None
12) 'X, if you are okay squeeze my hand 2 times' Response (circle one):	Time: _____:_____ Definite Indeterminate None
Signs of Distress/Arousal? (tachycardia, sweating, pupils, change in depth of anaesthesia, etc)	
BIS Value (post-commands)	
Remifentanil CE (post-commands)	mcg
Propofol CE (post- commands)	mcg
Save BIS Data to USB and Remove USB Key ☐	
Emergence Data	
Procedure Finish:	Time: _____:_____
Time of Extubation:	Time: _____:_____
Please return CRF to research staff or give to PACU staff to lock in cupboard. **Thank you.**	

Post-operative Data **Date of Assessment:**_____

15 minutes after arrival to PACU- Time: _____:_____

RASS Score	
Nu-DESC Score	
Anxiety Scale (1-10)	
Pain Score (1-10)	
PONV Score (0-none, 1- nausea, 2-vomiting)	

CAM-ICU 7

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

60 minutes after arrival to PACU- Time: _____:_____

RASS Score	
Nu-DESC Score	
Anxiety Scale (1-10)	
Pain Score (1-10)	
PONV Score (0-none, 1-nausea, 2-vomiting)	

CAM-ICU		
Items	**Grading**	**Score**
1. Acute Onset or Fluctuation of Mental Status Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	0 absent 1 present	
2. Inattention Say to the patient, "*I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand.*" Read letters from the following letter list in a normal tone 3 seconds apart. SAVEAHAART (Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A")	0 absent (correct ≥ 8) 1 for inattention (correct 4-7) 2 for severe inattention (correct 0-3)	
3. Altered Level of Consciousness Present if the Actual RASS score is anything other than alert and calm (zero)	0 absent (RASS 0) 1 for altered level (RASS 1, −1) 2 for severe altered level (RASS >1, < −1)	
4. Disorganized Thinking Yes/No Questions 1. Will a stone float on water? 2. Are there fish in the sea? 3. Does one pound weigh more than two pounds? 4. Can you use a hammer to pound a nail? Errors are counted when the patient incorrectly answers a question. Command: Say to patient "Hold up this many fingers" (Hold two fingers in front of patient). "Now do the same with the other hand" (Do not repeat number of fingers) An error is counted if patient is unable to complete the entire command.	0 absent (correct ≥ 4) 1 for disorganized thinking (correct 2, 3) 2 for severe disorganized thinking (correct 0, 1)	
	Total Score	

Nu-DESC:

Time / Period / Symptom	15 minutes after admission into PACU	60 minutes after admission into PACU
I. Disorientation Verbal or behavioral manifestation of not being oriented to time or place or misperceiving persons in the environment • **Last name? Location? Year? Why here?**		
II. Inappropriate Behavior Behavior inappropriate to place and/or for the person; e.g. puling at tubes or dressings, attempting to get out of bed when that is contraindicated, and the like.		
III. Inappropriate Communication Communication inappropriate to place and/or for the person; e.g., incoherence, non-communicativeness, nonsensical or unintelligible speech.		
IV. Illusions/Hallucinations Seeing or hearing things that are not there; distortions of visual objects. • **In the last few minutes, have you seen or heard things that are not really there?** • **Is your vision or hearing distorted?**		

V. Psychomotor retardation Delayed responsiveness, few or no spontaneous actions/words; e.g., when the patient is prodded, reaction is deferred and/or the patient is unarousable.		
Total Score		

GUIDELINES TO SCORING:

DISORIENTATION:
0 = No signs of item present. Patient is orientated to time place and person.
1 = Mild to moderate, barely expressed and noticeable through to being present and undeniable. Patient still can provide some orientating information to time, place and/or person.
2 = Moderate to severe: patient is not orientated to time or place. I,e in severe impairment will be not able to tell you the date, month, day, year, season, floor, name of hospital, city, state, and country.

INAPPROPRIATE BEHAVIOUR:
0 = no signs of item present
1 = mild to moderate: Hyperactivity is barely noticeable or appears as simple restlessness, to undeniable, subject moves frequently.
2 = moderate to severe: Hyperactivity is severe; patient is constantly moving, overreacts to stimuli, requires surveillance and/or restraint

INAPPROPRIATE COMMUNICATION;
0 = no sign of items present: patient's speech is coherent and goal-directed
1 = mild to moderate: patient's speech is slightly difficult to follow; responses to questions are slightly off target, to disorganized speech being clearly present
2 = moderate to severe: conversation is impossible due to severely disorganized thinking or speech (e.g rambling, irrelevant, or incoherent speech, or by tangential, circumstantial, or faulty reasoning)

ILLUSIONS/HALLUCINATIONS:
0 = no sign of items present
1 = mild to moderate: misperceptions or illusions related to sleep, fleeting hallucinations
2 = moderate to severe: frequent or intense illusions or hallucinations that disrupts care, function or is associated with inappropriate behaviour.

PSYCHOMOTOR RETARDATION:
0 = no sign of items present
1 = mild to moderate: Hypoactivity is barely noticeable, expressed as slightly slowing of movement, to moderate slowing of movements.
2 = moderate to severe: Hypoactivity is severe; patient does not move or speak without prodding or is catatonic

24-Hour Post-operative Follow Up

Date of follow up: _____ *Time of follow up:* _____

At any stage after the operation, did you have the following (please check one box for each question 1-10):

	No	Yes, Moderate	Yes, Severe
1. Drowsiness	☐	☐	☐
2. Pain at the site of surgery	☐	☐	☐
3. Thirst	☐	☐	☐
4. Hoarseness	☐	☐	☐
5. Sore throat	☐	☐	☐
6. Nausea or vomiting	☐	☐	☐
7. Feeling cold	☐	☐	☐
8. Confusion or disorientation	☐	☐	☐
9. Pain at the site of the anesthetic injection	☐	☐	☐
10. Shivering	☐	☐	☐

	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied	N/A
11. How satisfied were you with the information you were given by the anesthetist before the operation?					
12. How satisfied were you waking up from anesthesia?					
13. How satisfied have you been with pain therapy after surgery?					
14. How satisfied were you with treatment of nausea and vomiting after the operation?					
15. How satisfied were you with the					

care provided by the department of anesthesia in general?					
16. Would you recommend this anesthetic service to friends and family?	Yes ☐ No ☐				

17. What is the last thing you remember before going to sleep (please check one box)?

☐	Being in the pre-operative area
☐	Seeing the operating room
☐	Being with family
☐	Hearing voices
☐	Feeling mask on face
☐	Smell of gas
☐	Burning or stinging in the IV line
☐	Other:

18. What is the first thing you remember after waking up (please check one box)?

☐	Hearing voices
☐	Feeling breathing tube
☐	Feeling mask on face
☐	Feeling pain
☐	Seeing the operating room
☐	Being in the recovery room
☐	Being with family
☐	Being in the intensive care unit
☐	Nothing
☐	Other:

19. Do you remember anything between going to sleep and waking up (please check <u>ALL</u> relevant boxes)?

☐	No
☐	Yes; Hearing voices
☐	Yes; being asked to squeeze the hand of the research staff
☐	Yes; Hearing events of the surgery

☐	Yes; being unable to move or breathe
☐	Yes; anxiety/stress
☐	Yes; feeling pain
☐	Yes; Sensation of breathing tube
☐	Yes; Feeling surgery without pain
☐	Yes; Other:

20. Did you dream during your procedure (please check one box)?

☐	No
☐	Yes; Please describe:

21. Were these dreams disturbing to you (please check box)?	☐ Yes ☐ No

22. What was the worst thing about your operation (please check one box)?

☐	Anxiety
☐	Pain
☐	Recovery Process
☐	Unable to carry out usual activities
☐	Awareness
☐	Other:

Thank you for taking the time to complete this questionnaire.

7-Day Post-operative Follow-Up

Date of follow up: _____ Time of follow up: ____:_____

At any stage after the operation, did you have the following (please check one box for each question 1-10):

	No	Yes, Moderate	Yes,Severe
1. Drowsiness	☐	☐	☐
2. Pain at the site of surgery	☐	☐	☐
3. Thirst	☐	☐	☐
4. Hoarseness	☐	☐	☐
5. Sore throat	☐	☐	☐
6. Nausea or vomiting	☐	☐	☐
7. Feeling cold	☐	☐	☐

8. Confusion or disorientation	☐		☐		☐
9. Pain at the site of the anesthetic injection	☐		☐		☐
10. Shivering	☐		☐		☐
	Very Satisfied	Satisfied	Dissatisfied	Very Dissatisfied	N/A
11. How satisfied were you with the information you were given by the anesthetist before the operation?					
12. How satisfied were you waking up from anesthesia?					
13. How satisfied have you been with pain therapy after surgery?					
14. How satisfied were you with treatment of nausea and vomiting after the operation?					
15. How satisfied were you with the care provided by the department of anesthesia in general?					
16. Would you recommend this anesthetic service to friends and family?	☐ Yes ☐ No				

17. What is the last thing you remember before going to sleep (please check one box)?

☐	Being in the pre-operative area
☐	Seeing the operating room
☐	Being with family
☐	Hearing voices
☐	Feeling mask on face
☐	Smell of gas
☐	Burning or stinging in the IV line
☐	Other:

18. What is the first thing you remember after waking up (please check one box)?

☐	Hearing voices
☐	Feeling breathing tube
☐	Feeling mask on face
☐	Feeling pain
☐	Seeing the operating room
☐	Being in the recovery room
☐	Being with family
☐	Being in the intensive care unit

☐	Nothing
☐	Other:

19. Do you remember anything between going to sleep and waking up (please check <u>ALL</u> relevant boxes)?

☐	No
☐	Yes; Hearing voices
☐	Yes; being asked to squeeze the hand of the research staff
☐	Yes; Hearing events of the surgery
☐	Yes; being unable to move or breathe
☐	Yes; anxiety/stress
☐	Yes; feeling pain
☐	Yes; Sensation of breathing tube
☐	Yes; Feeling surgery without pain
☐	Yes; Other:

20. Did you dream during your procedure (please check one box)?

☐	No
☐	Yes; Please describe:

21. Were these dreams disturbing to you (please check box)?	☐ Yes ☐ No

22. What was the worst thing about your operation (please check one box)?

☐	Anxiety
☐	Pain
☐	Recovery Process
☐	Unable to carry out usual activities
☐	Awareness
☐	Other:

Thank you for taking the time to complete this questionnaire.

Appendix 2.

Pre-operative Questionnaire for Females

8. What is your current contraception if any?

[ ] None

[ ] Fertility awareness /withdrawal method

[ ] Condoms/cap/diaphragm

[ ] Combine oral contraceptive pill*

[ ] Progesterone only pill*

[ ] Contraceptive implant (implanon/Nexplanon)

[ ] Contraceptive intrauterine device (non hormonal)

[ ] Contraceptive intrauterine device (hormonal)

[ ] Sterilisation

*If you take a contraceptive pill have you missed any pills in the last week? Yes/No

9. Do you take any form of hormone therapy or replacement? Yes/No

Please specify medication:

10. Do you have regular periods? (please tick one box)
- Yes
- No, they have never been regular
- No, they have been irregular for a few months
- No, my periods have stopped

11. What is the usual interval between the start of one period and the start of your next period (cycle length)? _____days

12. How long do your periods usually last for? _____days

13. When was your last period? Please fill in the date of the first day of your last period (dd/mm/yy)

14. If you your periods have stopped, what best describes the reason you have not had a period in the last 12 months? (please tick one box)

- Menopause
- Currently pregnant
- Currently breast feeding
- Contraceptives e.g. hormonal IUD, contraceptive implants
- Medical e.g. medication, chemotherapy, radiotherapy
- Surgical e.g. uterus removed, ovaries removed, ablation (novasure)
- Other: please describe_____