VOLATILE VS TOTAL INTRAVENOUS ANAESTHESIA

PROTOCOL

Volatile vs Total intravenous Anaesthesia for major non-cardiac surgery: A pragmatic randomised triaL (VITAL)

ISRCTN Number	ISRCTN62903453
Sponsor	University of Warwick
Funding Body	National Institute for Health Research Health Technology Assessment
Sponsor reference	SOC.19/20-21
Funder reference	NIHR130573
Ethics Approval	Yorkshire and The Humber – Bradford Leeds Research Ethics Committee, 30 Sep 2021, Ref: 21/YH/0162
Version Number	3.0
Date	10 Aug 2023
Stage	Final

This protocol has regard for current HRA guidance and content

Protocol Amendments:

Amendment No.	Date of Amendment	Date of Approval
SA 1.0	9th February 2023	1st March 2023
SA 2.0	25th August 2023	13th September 2023

FUNDED BY NIHR | National Institute for Health Research

This project is funded by the National Institute for Health Research (NIHR) HTA programme [NIHR130573]. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

CONTACT NAMES AND NUMBERS

Role	Name, address, telephone
Sponsor:	Carole Harris University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 575733 Email: sponsorship@warwick.ac.uk
Chief Investigator:	Dr Joyce Yeung Warwick Clinical Trials Unit University of Warwick Gibbet Hill Road Coventry, CV4 7AL Tel: 02476 73357 Email: j.yeung.4@warwick.ac.uk
Co-Chief Investigator:	Dr Shaman Jhanji Critical Care Unit Royal Marsden Hospital Fulham Road London, SW3 6JJ4 Tel: 0207 8118059 Email: shaman.jhanji@rmh.nhs.uk
Senior Project Manager:	Dalbir Kaur Warwick Clinical Trials Unit University of Warwick Email: dalbir.kaur@warwick.ac.uk
Trial Manager:	Claire Jacques Warwick Clinical Trials Unit University of Warwick Tel: 02476 522566 Email: VITAL@warwick.ac.uk

Co-investigators:	Professor Janet Dunn Warwick Clinical Trials Unit University of Warwick Email: j.a.dunn@warwick.ac.uk Professor Ramani Moonesinghe Centre for Anaesthesia, Critical Care & Pain Medicine University College London Email: ramani.moonesinghe@nhs.net Professor Rupert Pearse Barts and The London School of Medicine & Dentistry Queen Mary University of London Email: r.pearse@qmul.ac.uk Dr Ben Shelley Academic Unit of Anaesthesia, Pain and Critical Care Medicine University of Glasgow Email: benjamin.shelley@glasgow.ac.uk Dr Cecilia Vindrola Department of Applied Health Research University College London Email: c.vindrola@ucl.ac.uk Patient & Public co-investigators: Mr John Braun (PPI) Ms Monica Jefford (PPI)
Statistician:	Dr Louise Hiller Warwick Clinical Trials Unit (WCTU) University of Warwick Email: l.hiller@warwick.ac.uk
Health Economist:	Professor James Mason Warwick Clinical Trials Unit (WCTU) University of Warwick Email: j.mason@warwick.ac.uk
Trial Steering Committee:	A list of members and contact details can be found in the Trial Master File

Data Monitoring Committee:	A list of members and contact details can be found in the Trial Master File

For general queries and supply of trial materials please contact the coordinating centre:

Warwick Clinical Trials Unit (WCTU)

The University of Warwick

Gibbet Hill Road

Coventry

CV4 7AL

Tel: 02476 522566

Email: vital@warwick.ac.uk

Website: www.warwick.ac.uk/vital

TABLE OF CONTENTS **PAGE**

LIST OF TABLES PAGE

LIST OF FIGURES PAGE

TRIAL SUMMARY

Trial Title	Volatile vs Total intravenous Anaesthesia for major non-cardiac surgery: A pragmatic randomised triaL	
Internal ref. number (or short title)	VITAL	
Clinical Phase	Phase III	
Trial Design	A multi-centre pragmatic efficient randomised trial with health economic evaluation	
Trial Participants	Adults aged 50 years and over, undergoing elective major non-cardiac surgery under general anaesthesia	
Planned sample size	2500	
Treatment Duration	For the duration of general anaesthesia for surgery	
Follow-up Duration	6 months	
Planned Trial Period	54 months	
	Objectives	Outcome Measures
Primary	To test whether TIVA is superior to inhalational volatile-based anaesthesia in terms of days alive and at home at 30 days (DAH30), survival and quality of recovery amongst patients undergoing major non-cardiac surgery	• Days alive and at home at 30 days (DAH30)
Secondary	To evaluate the clinical effectiveness and safety of TIVA	• Days alive and at home at 90 days (DAH90) • 30-day, 90-day, 6-month mortality • Quality of recovery after anaesthesia (QoR15) • Patient satisfaction with anaesthesia (Bauer questionnaire) • Health-related quality of life (EQ-5D) • Accidental awareness under anaesthesia (modified Brice questionnaire) • Postoperative complications
	To assess the cost-effectiveness of TIVA	• Health resource use during the six months after surgery

LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AUC	Area Under the Curve
AWR	Accidental awareness under anaesthesia with explicit recall
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CI	Chief Investigator
CONSORT	*Con*solidated *S*tandards *o*f *R*eporting *T*rials
CRF	Case Report Form
CTU	Clinical Trials Unit
DAH	Days Alive and at Home
DMC	Data Monitoring Committee
eCRF	electronic Case Report Form
GCP	Good Clinical Practice
ICF	Informed Consent Form
IRAS	Integrated Research Application System
ISRCTN	International Standard Randomised Controlled Trial Number
IVRS	Interactive voice response randomisation system
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PI	Principal Investigator
POMCTN	Perioperative Medicine Clinical Trials Network
PPI	Patient & Public Involvement
PQIP	Perioperative Quality Improvement Programme
QoL	Quality of Life
QoR	Quality of Recovery
QALY	Quality Adjusted Life Year
RAP	Rapid Assessment Procedures
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
R&D	Research and Development
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

SWAT	Study within a Trial
TMG	Trial Management Group
TSC	Trial Steering Committee
TIVA	Total Intravenous Anaesthesia
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor
WCTU	Warwick Clinical Trials Unit
WMS	Warwick Medical School

1.1 Epidemiology and burden of general anaesthesia for major surgery

We perform more than 1.5 million major non-cardiac surgeries in the NHS each year, including a variety of procedures from cancer resections to orthopaedic surgery.[1] High-quality general anaesthesia is essential for patients undergoing major surgery. In the NHS, general anaesthesia is most often maintained with an inhaled volatile anaesthetic agent (e.g. sevoflurane, isoflurane).[2] A commonly used alternative is to maintain anaesthesia using infusions of intravenous anaesthetic drugs (e.g. propofol, remifentanil), a technique termed total intravenous anaesthesia or TIVA. The two techniques have important differences in side effect profile.[3,4] Many anaesthetists believe TIVA is just as safe as inhalational anaesthesia and provides better and faster immediate patient recovery with reduced nausea and vomiting, reduced acute pain and quicker wakening from anaesthesia. However, others are not convinced that TIVA meaningfully improves patient recovery and are concerned about serious but rare risks such as accidental awareness, where patients are aware of their surroundings during surgery.[5] There is a distinct lack of data describing the benefits and harms of either technique in terms of important patient outcomes. More recently, low-grade evidence suggesting reduced cancer recurrence and fewer greenhouse gas effects with TIVA has accelerated the adoption of this technique by NHS anaesthetists.[6-8] [9]

Given the very large number of patients exposed to general anaesthesia every year, even small differences in outcome between the two techniques could result in substantial excess harm. Our proposed randomised trial will quantify the benefits and harms of each technique in terms of patient recovery, survival and safety. Our results will ensure patients can benefit from the very safest anaesthesia care, promoting an early return home, reducing healthcare costs and maximising the health benefits of surgical treatments.

1.2 Existing knowledge

Whilst the clinical endpoint of general anaesthesia is broadly similar between inhalational anaesthesia and TIVA, their underlying pharmacological actions are very different. Propofol (an intravenous anaesthetic drug used to provide TIVA) and inhalational hydrocarbon-based anaesthetic gases are both recognised to mediate general anaesthesia via the $GABA_A$ receptor in the brain, but it is increasingly understood that general anaesthesia is the product of action on many different neuronal receptors rather than via a single mechanism.[10] Both inhalational and TIVA agents have wide-ranging and differing interactions with a host of other molecular targets including potassium and voltage-gated ion channels, and glycine receptors.[10-12] One of the suggested benefits of inhalational anaesthesia is suppression of pro-inflammatory mediators that reduce the systemic inflammatory response to the tissue injury caused by surgery. [13-15] In addition, animal studies and observational human studies suggest inhalational anaesthesia may have cardioprotective properties during surgery.[16]

I. Patient Safety

There is concern amongst clinicians that TIVA is associated with a higher incidence of accidental awareness under anaesthesia with explicit recall (AWR) due to inability to routinely monitor for intravenous anaesthetic levels.[17-19] A major national audit by the Royal College of Anaesthetists found that awareness was more frequent with TIVA, although most cases were considered preventable.[20] National Institute for Health and Care Excellence (NICE) guidance did not consider patients receiving TIVA are at higher risk of AWR but nevertheless recommended the use of depth of anaesthesia monitoring as an option for patients undergoing TIVA (NICE DG6, 2012). Despite this recommendation, the uptake of current generations of processed electroencephalographic monitors by the anaesthetic community has remained low in the UK.[21] The VITAL trial will examine the rates of accidental awareness under anaesthesia between TIVA and inhalational anaesthesia.

II. Environmental Impact

Concerns for environmental impact of inhalational anaesthetic agents have driven some anaesthetists to adopt a TIVA technique. Inhalational drugs undergo little metabolism during clinical application and are expelled almost completely unchanged to the atmosphere. A rapid accumulation and increase in the amount of inhalational anaesthetic agents (isoflurane, desflurane and sevoflurane) has been detected in the global atmosphere, estimated at 3.1 ± 0.6 million tonne CO_2 equivalent in 2014.[22] The use of inhalational anaesthetic agents contributes to the greenhouse effect and their potential to destroy stratospheric ozone associated with their long atmospheric lifetimes. It is estimated that they contribute 2.5% of the NHS carbon footprint.[23] Whilst TIVA does not use inhalational anaesthetic agents, its main drug propofol, does not degrade and is toxic to aquatic life. The environmental impact of TIVA is less clear and there is little data regarding the environmental impact of the manufacture, delivery (including single use plastic syringes) and disposal of propofol.[24]

III. Is TIVA associated with reduced cancer recurrence?

There is emerging evidence suggesting anaesthetic technique may affect disease-free survival amongst patients undergoing cancer surgery. A large retrospective analysis performed by one of our co-applicants examined the impact of anaesthesia on outcomes following cancer surgery amongst 5214 patients in the UK found that TIVA was associated with improved disease-free cancer survival compared to inhalational anaesthesia.[6] Similar signals of benefit for TIVA were reported in other observational studies. [25-27] Surgical resection can provide complete removal of primary tumour and potential cure for many cancer patients. However, despite apparently complete tumour resection, disease progression can occur in up to a third of patients. Manipulation of tumour combined with the relatively immunosuppressed state as a result of surgical

stress and general anaesthesia is believed to lead to seeding of metastases and paradoxical disease progression.[28,29] There is recent preclinical evidence indicating that the systemic inflammatory response and immune disequilibrium following surgery can allow growth of metastases, highlighting the potentially important role of drugs used in the perioperative period which may directly affect cancer cells and or the immune response to surgery.[30,31] Small mechanistic studies have suggested TIVA can prevent immunosuppression and inhibit cancer cell migration.[31,32] These in vitro studies along with observational data have persuaded some clinicians to abandon the use of inhalational anaesthesia in cancer surgery. Results from recent clinical studies have so far not demonstrated any benefit of anaesthetic techniques in cancer outcomes following surgery.[33]

IV. Systematic reviews

In our literature search we found 11 systematic reviews and five Cochrane reviews that compared different aspects of intravenous and inhalational anaesthesia. Two systematic reviews which examined impact of anaesthetic techniques on long term cancer outcomes suggested with low certainty that TIVA may be beneficial.[34,35] Two systematic reviews compared complications and mortality of anaesthetic techniques in cardiac surgery patients only and found no differences in peri-operative complications or survival.[36,37] Eight other systematic reviews compared anaesthetic techniques in selected surgical groups: neurosurgery [38,39]; one lung ventilation in thoracic surgery [40,41]; robotic assisted laparoscopic surgery [42]; paediatric surgery [43,44]; ambulatory/day case surgery.[44,45] These eight systematic reviews provide the existing evidence for the majority of patients undergoing major non-cardiac surgery and assessed various aspects of recovery immediately after surgery such as speed of recovery of consciousness, nausea and vomiting and acute pain. The findings suggest TIVA is associated with faster recovery of consciousness, a reduced risk of nausea and vomiting and less pain immediately after surgery. [46-48] A 2018 Cochrane review suggests a reduced risk of post-operative cognitive dysfunction for older patients undergoing non-cardiac surgery with TIVA.[49] However, the authors were unable to draw conclusions regarding patient survival because component trials were small with a high risk of bias (three studies, 271 patients).

Crucially these systematic reviews did not provide evidence on patient-centred outcomes or safety outcomes such as accidental awareness during anaesthesia. We performed a literature search for relevant randomised trials comparing the effect of intravenous and inhalational anaesthesia on key patient outcomes. A comprehensive literature search of Medline, EMBASE and Cochrane Libraries was conducted using the terms (volatile[All Fields] OR inhalational[All Fields]) AND ("anaesthesia"[All Fields] OR "anesthesia"[MeSH Terms] OR "anesthesia"[All Fields]) AND versus[All Fields] AND ("propofol"[MeSH Terms] OR "propofol"[All Fields]). Search date was from database inception to 10th January 2020. We identified only one large trial in non-

cancer patients. The MortalitY in caRdIAc surgery trial (MYRIAD), which included 5400 patients undergoing cardiac surgery who were randomised to TIVA or inhalational anaesthesia. This trial was designed to specifically test whether inhalational anaesthesia was protective against myocardial injury and reduced mortality in patients undergoing cardiac surgery.[9] The trial was stopped early for futility with similar one-year mortality rates in both groups. By recruiting only patients undergoing cardiac surgery, this trial did not address uncertainty for the greater majority, more than 1.5 million of surgical patients. Consequently, the MYRIAD trial does not inform the care for the overwhelming majority of NHS surgical patients. Furthermore, MYRIAD investigators focused their study on all-cause mortality and did not measure important patient-focused outcomes in terms of patient recovery and safety.

1.3 Hypothesis

In adult patients (aged≥50 years) undergoing major non-cardiac surgery, does total intravenous anaesthesia (TIVA) lead to improved patient outcomes compared to inhalational volatile-based anaesthesia.

1.4 Need for a trial

Improving outcomes after surgery is a major public health research priority for patients, clinicians and the NHS.[50,51] The greatest burden of perioperative complications, mortality and healthcare costs lie amongst the population of patients aged over 50 years who undergo major non-cardiac surgery. Apart from the recent study in specialist cardiac surgery, there is no major trial to define the optimal anaesthetic technique. Cardiac surgery represents only a small proportion of surgical activity in the NHS; 35,000 patients per year compared to more than 1.5 million patients undergoing non-cardiac surgery each year.[1] The lack of robust evidence means that neither TIVA nor inhalational anaesthesia can be recommended as standard care for the vast majority of patients. Patients may therefore be exposed to avoidable harm. The choice of anaesthesia not only affects the care of patients during surgery but may also impact on their quality of recovery, survival and other patient safety outcomes, including awareness under anaesthesia. Prompt recovery and discharge from hospital will enhance physical recovery, limiting immobility and physical deconditioning.[52,53] These aspects are of growing importance as frail older patients now undergo major surgery more often than ever before.[54,55] Improving recovery and reducing complications post-surgery are ranked as one of the top James Lind Alliance research priorities for both patients and clinicians.[51] The VITAL trial specifically examines the effect of anaesthetic technique on key patient outcomes: speed and quality of recovery after surgery (quality of recovery after anaesthesia, patient satisfaction and major post-operative complications), survival and patient safety. With our patient representatives, we have chosen Days alive and at home up to 30 days after surgery (DAH30) as a patient-centred, well-validated and measurable outcome.[56,57] If improved anaesthetic care could

reduce hospital stay by just one day, the NHS would save £343 million each year whilst releasing in-patient beds for other patients to undergo surgery sooner.[58]

1.5 Ethical considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and University of Warwick Standard Operating Procedures (SOPs). All data will be stored securely and held in accordance with Data Protection Act 2018.

VITAL is a data-efficient trial and is being run in collaboration with the Royal College of Anaesthetists (RCoA). As a result, VITAL will be utilising the Perioperative Quality Improvement Programme (PQIP) data collection platform with the addition of some added data collection fields. In order to manage this for the duration of the trial, data will be exported from the PQIP database and imported into the VITAL web application. This poses a potential ethical and trial management risk due to the practicalities of data processing above and beyond usual practice, with the added nuances of the University of Warwick and the RCoA acting as joint data controllers. These risks have been minimised by explicitly stipulating the data collection processes and expected processing activities in the collaboration agreement between both parties. Additional validation testing of the export/import process will be in place prior to recruitment to VITAL, and checks have been allocated in the Data Management Plan to monitor data exchanging activities between the two databases.

1.6 CONSORT

The trial will be reported in line with the CONSORT (*Con*solidated *S*tandards *o*f *R*eporting *T*rials) statement (Lancet 2001, **357**: 1191-1194, www.consort-statement.org).

2. TRIAL DESIGN

2.1 Trial setting

The trial will take place in approximately 40 NHS hospitals. Potentially eligible participants will be identified through surgical and joint multidisciplinary meetings, pre-operative assessment clinics and/or theatre lists at participating centres.

2.2 Trial summary

VITAL is a multi-centre pragmatic randomised trial comparing the clinical and cost effectiveness of TIVA and inhalational anaesthesia (Figure 1). We propose an efficient trial design led by the Peri-Operative Medicine

Clinical Trials Network (pomctn.org.uk) and partnering with an existing national cohort study hosted by the Royal College of Anaesthetists: the Perioperative Quality Improvement Programme, PQIP. Using PQIP's prospective clinical dataset and existing NHS data sources, we will limit the burden of research for participants and data collection requirements. Due to the utilisation of the PQIP dataset, all VITAL participants must also be taking part in PQIP.

2.3 Internal pilot (six months)

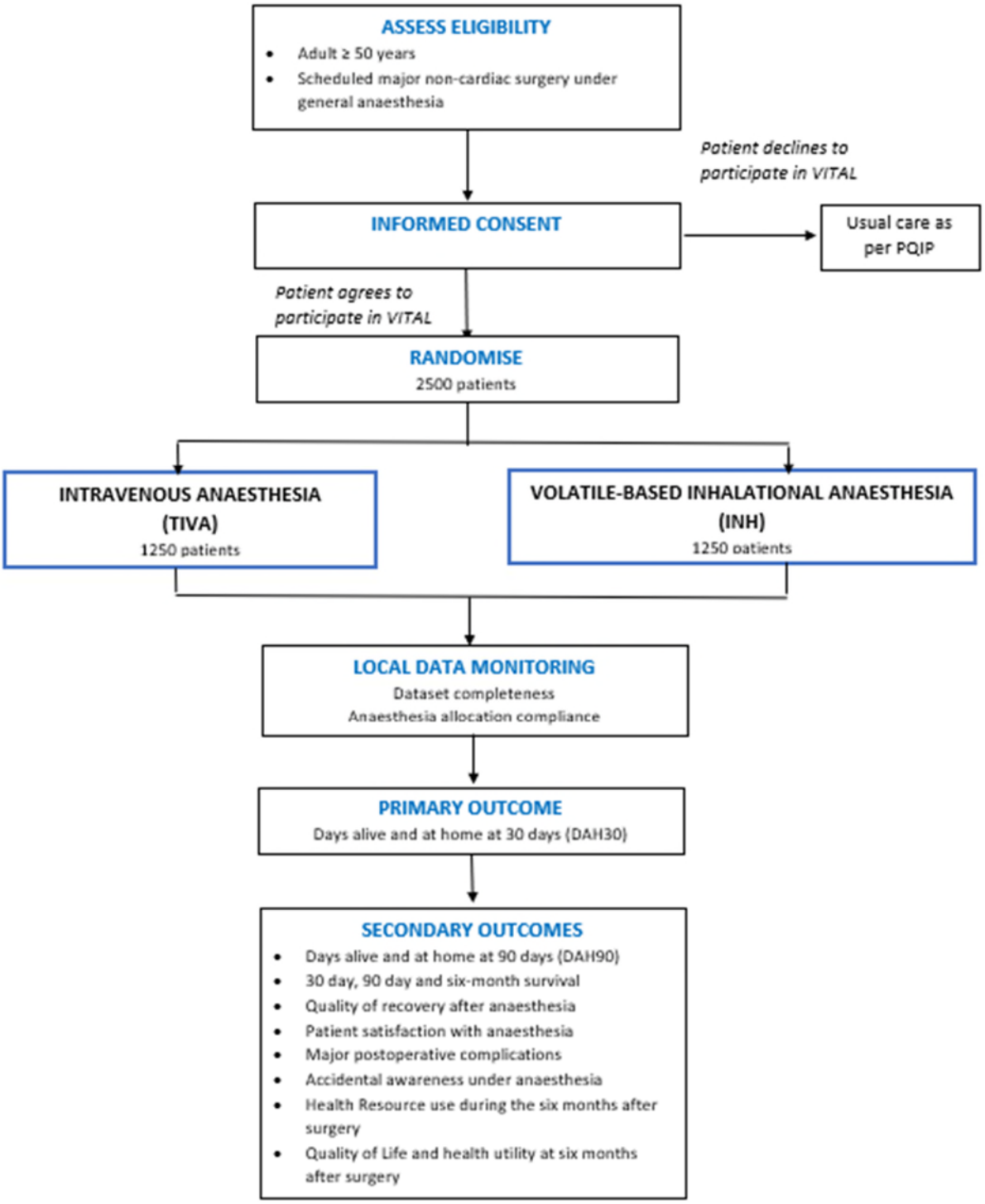
For a six-month internal pilot phase, our target recruitment will be 2-3 participants per site per month open to recruitment (see Table 1). Allowing for a staggered start to opening at least 10 sites, we anticipate 105 participants will be recruited in the first six months. Protocol compliance and the completeness of primary outcome data will be reviewed by the TSC noting that six-month follow-up data will not be completed by the end of the pilot. On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial. Results from the pilot will be reported in the HTA Monograph in accordance with the CONSORT guidelines for pilot studies.

A qualitative Study Within A Trial (SWAT) will investigate the benefits and barriers to consenting and recruiting participants to two complementary studies (PQIP and VITAL). A separate study protocol has been provided for the SWAT, available upon request from the VITAL research team. The SWAT is registered on the SWAT repository hosted by the Northern Ireland Network for Trials Methodology Research (http://go.qub.ac.uk/SWAT-SWAR),; reference number; 165.

Table 1 **Pilot trial success criteria for recruitment**

Target	Red	Amber	Green
Trial recruitment	<60%	60-99%	≥100%
Recruitment rate (per site per month)	<1.5	1.5-1.9	≥2.0
Number of sites open	<6	6-9	≥10
Indicative number of participants recruited	<63	63-104	≥105
Decision	Decision to progress will be made by the TSC in association with the funder.	Progress to main trial with additional sites being recruited as well as a screening log and protocol review.	Progress to main trial following a review of screening logs and protocol. Any barriers to recruitment will be addressed

Figure 1 **Trial flow diagram**



2.4 Aims and objectives

2.4.1 Primary objective

The primary objective of this trial is to test whether TIVA is superior to inhalational anaesthesia in terms of days alive and at home at 30 days (DAH30), survival and quality of recovery amongst patients undergoing major non-cardiac surgery.

2.4.2 Secondary objectives

- To evaluate the safety of TIVA, including post-operative complications and incidence of accidental awareness under anaesthesia.
- To assess the cost-effectiveness of TIVA.

2.5 Outcome measures

2.5.1 Effectiveness

Primary outcome

The primary outcome is Days alive and at home at 30 days after surgery (DAH30). DAH30 is a continuous number between 0 and 30, reflecting the total number of days that a patient spends alive and at home within 30 days after surgery. In this definition, home reflects any place other than hospital. If a patient dies within those 30 days, their value is set to 0.

Secondary outcomes

- Days alive and at home at 90 days (DAH90)
- 30-day and 90-day mortality
- Six-month mortality
- Quality of recovery after anaesthesia (QoR-15) at day three after surgery [59]
- Patient satisfaction with anaesthesia (Bauer questionnaire) on day one after surgery [60]

2.5.2 Safety

- Accidental awareness under anaesthesia (modified Brice questionnaire) on day three and 30 days after surgery [61]
- Major post-operative complications Clavien-Dindo Grade 2 and above within 30 days after surgery [62](Appendix A)

2.5.3 Health economics

- Health resource use during the six months after surgery
- Health-related quality of life evaluated using EuroQoL instrument (EQ-5D-5L) at baseline, at hospital discharge, at 30 days and six months after surgery [63,64]

2.6 Eligibility criteria

Participants are eligible to be included in the trial if they meet the following criteria:

2.6.1 Inclusion criteria

1. Age ≥ 50 years
2. Elective major non-cardiac surgery under general anaesthesia (as per PQIP inclusion criteria)
3. Written informed consent for trial participation

2.6.2 Exclusion criteria

1. Known contraindication to either TIVA or inhalational anaesthesia
2. Clinician refusal
3. Procedures where the participant is not expected to survive for 30 days
4. Previous participation in VITAL trial
5. Patient unable to give informed consent or complete questionnaires

2.7 Participant identification / Screening

During the trial recruitment period, hospital research teams will liaise with clinical staff to identify individuals with upcoming major non-cardiac surgery that may be eligible for enrolment. Based on this referral, a member of the team delivering the trial at the hospital (e.g. clinician, nurse or research practitioner) with appropriate knowledge will formally assess eligibility of the participant against trial inclusion and exclusion criteria. No additional tests or investigations will be required for assessing eligibility.

2.7.1 Site Staff Training

Each centre will have a named consultant-level investigator who will lead recruitment and who will be the Principal Investigator (PI). The local members of research team will be accountable to these PIs. The CI, co-CI and Trial Manager/Coordinator will provide trial-specific training to all centres prior to site initiation and subsequently as required to ensure consistency of practice across all sites. Sites will be provided with access

to the Interactive Voice Response Randomisation System (IVRS) once training is completed, the green light has been provided and all approvals are in place.

2.7.2 Informed consent

Potential participants will be screened by research staff at the site having been identified from pre-admission clinic lists, operating theatre lists and by communication with the relevant nursing and medical staff. Before surgery, potential participants will be identified and approached by a member of the research team, who are considered part of the direct care team. This may be conducted via telephone, post, online or face-to-face consultations and provides an opportunity for the research team to explain the trial to the participants in detail. Patient information sheets can be posted or emailed to participants for their perusal and consideration. The participant will be approached prior to surgery at the first suitable opportunity to allow time for any questions. It is recommended (although not mandated) that the participant is approached at least one day prior to the date of surgery. Written informed consent must be obtained before surgery and can be obtained using either paper or electronic systems depending on individual sites arrangements. It is the responsibility of the Principal Investigator (PI) at each site, or persons delegated by the PI to obtain written informed consent from each potential participant prior to participation in this trial. This process will include provision of a patient information sheet accompanied by the relevant consent form, either paper or electronic, and an explanation of the aims, methods, anticipated benefits and potential hazards of the trial. The PI or designee will explain to all potential participants that they are free to refuse to enter the trial or to withdraw at any time during the trial, for any reason. If new safety information results in significant changes in the risk/benefit assessment, the patient information sheet and consent form will be reviewed and updated if necessary. The PI or designee will assess potential participant's capacity to give informed consent, and those who lack capacity to give or withhold informed consent will not be recruited. If a participant loses capacity during their participation in the trial, the original consent by the participant will be respected. If this situation occurs, clinical outcome data will continue to be collected, but participant questionnaires will not need to be completed. Patients who are not entered into this trial should be recorded (including reason not entered) on the electronic patient-screening log provided to sites in the Investigator Site File.

2.8 Randomisation

2.8.1 Randomisation

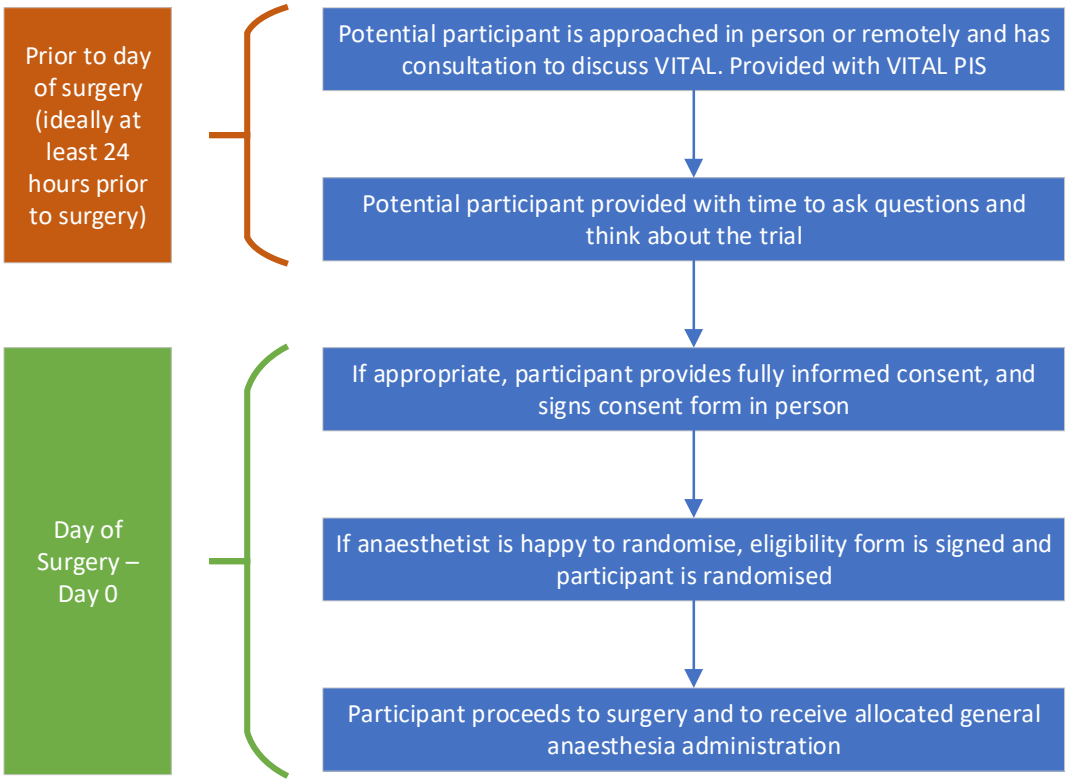
Participants will be randomised on a 1:1 basis to receive either TIVA or inhalational anaesthesia. Randomisation will be undertaken through a simple and secure, IVRS that has been established by the programming team at Warwick Clinical Trials Unit. This computerised procedure will use a minimisation algorithm to ensure balance in treatment arm allocation across the following four stratification variables,

factors thought to affect outcome either through treatment effectiveness or underlying prognosis, also permitting appropriate exploratory subgroup analyses:

1. Surgical speciality (musculoskeletal/intra-abdominal/thoracic/vascular/other)
2. Expected duration of surgery (<2hours, ≥2hours)
3. Cancer surgery/non-cancer surgery
4. Preoperative frailty (Rockwood Frailty Score) - Well/Vulnerable/Frail [65]

Should the IVRS be unavailable for technical reasons, an emergency randomisation system will be provided by WCTU Monday – Friday, 9am – 5pm. The emergency randomisation telephone number will be provided to sites in the Investigator Site Files.

Figure 2 Consent/Randomisation flow diagram



2.8.2 Randomising on day of surgery

Recruiting centres will be asked to randomise participants on the day of surgery, once the planned surgery is confirmed as taking place. There will be occasions when surgery is cancelled at the last minute and rescheduled to another day. If the participant is happy to remain in the trial, recruiting centres will be asked to inform the VITAL team at WCTU of the new surgery date as soon as possible, and data collection timepoints will be adjusted. Participants should receive their original allocated intervention at their new scheduled surgery date. If the surgery is cancelled indefinitely, or the participant is no longer suitable for the trial, the recruiting centre will be asked to inform the VITAL team at WCTU as soon as possible.

2.8.3 Post-randomisation withdrawals

Participants may withdraw from trial follow up at any time without prejudice. Data will be collected as per the trial protocol unless the participant has explicitly withdrawn their consent.

2.9 Trial treatments / intervention

Anaesthesia will be administered by experienced anaesthetists and delivered according to local guidelines. All other participant care will be conducted as per routine clinical practice. More detailed information regarding trial intervention will be provided to sites as part of the trial-specific training.

2.9.1 Total Intravenous Anaesthesia (TIVA)

Participants randomised to the TIVA arm of the trial will have their maintenance of anaesthesia performed with intravenous anaesthetic agents as determined by the treating anaesthetist. Administration of TIVA will not be protocolised and will be left to clinical discretion for management. Maintenance of general anaesthesia should be via TIVA only. During training, it will be emphasised that clinicians should not expose TIVA group participants to inhaled anaesthetic agents.

2.9.2 Volatile-based Inhalational Anaesthesia (INH)

Participants randomised to the INH arm of the trial will have their maintenance of anaesthesia performed with inhalational volatile-based anaesthetic agents as determined by the treating anaesthetist. Administration of INH will not be protocolised and will be left to clinical discretion for management. Maintenance of general anaesthesia should be via inhalational route only. During training, it will be emphasised that clinicians should not expose INH group participants to intravenous anaesthetic agents.

2.10 Minimising detection bias and contamination

2.10.1 Minimising outcome reporting bias

In this trial, it is not possible to blind patients or the research staff at sites to a patient's randomised allocation. The primary outcome and most of the clinically-reported secondary outcomes are objective. However, the clinically-reported secondary outcome of post-operative complications could include some degree of subjectivity. Therefore, to minimise reporting bias for this outcome, research teams will screen patient records for post-operative complications and use these records to determine those that have been confirmed/reported independently (e.g. pneumonia diagnosed from chest X-Ray reported by radiologist or by independent clinician). During the trial, the trial management group and the trial steering committee will not see outcome results broken down by treatment arm. Final analysis will occur once there has been time for all follow up data to be collected; the final statistical analysis plan has been signed off and data cleaning has occurred.

2.10.2 Cross over between treatment arms

It is possible that the participant may receive an anaesthesia technique other than the one that was allocated to them within the trial, for example due to equipment malfunction or change in clinical circumstances. In this case, we will still include the participant in the trial analysis on an intention-to-treat basis. However, we will do an additional per-protocol analysis including only patients who received their allocated intervention (as detailed in the statistical analysis plan). In this pragmatic trial, brief deviations or interruptions in the allocated anaesthesia technique lasting shorter than 20 minutes will not be interpreted as true cross over between treatment arms.

2.11 End of trial

The trial will end when 2500 participants have been randomised and the last participant has completed final follow-up. The trial will be stopped prematurely if:

- Mandated by the Ethics Committee
- Following recommendations from the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) or Sponsor
- Funding for the trial ceases
- Subject to TSC/funder recommendation, pilot success criteria have not been met

The Research Ethics Committee that originally gave a favourable opinion will be notified in writing within 90 days when the trial has been concluded or within 15 days if terminated early.

3. METHODS AND ASSESSMENTS

3.1 Schedule of delivery of intervention and data collection

Table 2 Trial assessments

Visit Window	**Day 0** Baseline	**Day 1[#]**	**Day 3[#]**	**Day of discharge[#]**	**Day 30** + 7 days	**Day 90** + 7 days	**6 months** ± 21 days
Informed consent	✓						
Medical history	✓						
Inclusion/exclusion criteria	✓						
Surgical speciality	✓						
Expected duration of surgery (<2hrs, ≥2hrs)	✓						
Cancer surgery/non-cancer surgery	✓						
Preoperative frailty (Rockwood Frailty Score)	✓						
Intervention	✓^						
Bauer questionnaire		✓^					
QoR-15			✓^				
Modified Brice questionnaire			✓		✓		
Post-operative delirium (4AT)			✓				
Post-operative complications (Clavien-Dindo Grade II and above)					✓^		
Length of stay*				✓^			
Survival status*					✓^	✓	✓
Hospital readmission*					✓	✓	✓
Health resource use							✓
Quality of Life EQ 5D	✓^			✓^	✓^		✓^

*Information needed for DAH30 and DAH90

^ Already collected by PQIP database

[#] Or closest next working day

3.2 Follow-up assessments

Participants will be contacted by telephone at Day 30 (+ 7 days) by site research staff to screen for late recall of accidental awareness, collect data on EQ-5D-5L, hospital readmission and any post-operative complications that classed as Clavien-Dindo Severity Grade II or above (Appendix A & B). Day 90 (+ 7 days) follow up will be completed by a check of medical records only. Participants will be contacted by telephone at six months post-surgery (± 21 days) by site research staff to collect data on health resource use based on participant diary and quality of life using EQ-5D-5L. In the rare event that the participant was discharged home early, the site research team may contact the participant by telephone to complete questionnaires.

3.3 Modified Brice Questionnaire

Modified Brice Questionnaire is used to screen for recall of accidental awareness under general anaesthesia (AAGA). A potential case of AAGA should be flagged by the local research team if a patient responds that they remembered something between going to sleep and waking up, or they answered "Awareness" to the question asking them to report the worst thing about their operation. The Principal Investigators for each of these patients should be contacted by the local research team and asked to give their opinion of the likelihood of AAGA for their patients as "probable", "possible", "unlikely" or "un-assessable" according to previously defined criteria, (Appendix C) and using available local data. All cases of probable and possible AAGA should be reported to WCTU by completion of the Brice Questionnaire Additional Data Form. Patients should be followed up locally as per usual care.

4. ADVERSE EVENT MANAGEMENT

4.1 Definitions

4.1.1 Adverse Events (AE)

An Adverse Event (AE) is defined as any untoward medical occurrence in a trial participant, and which does not necessarily have a causal relationship with the treatment/intervention.

4.1.2 Serious Adverse Events (SAEs)

A Serious Adverse Event is an AE that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening

- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect
- Immediate intervention was required to prevent one of the above or is an important medical condition.

4.2 Assessing and Reporting Post-operative Complications, AEs, SAEs and related SAEs

Adverse events

VITAL is a non-CTIMP trial and all trial interventions are already in routine clinical use for patients undergoing major non-cardiac surgery. Expected Post-operative complications (starting from end of surgery on Day of surgery to 30 days post surgery) will be collected as a trial outcome and will not be recorded separately as AEs. These events will be included as part of the safety analysis for the trial and therefore do not need to be reported separately to the Trial Coordinating Centre. No additional AEs will be collected, other than those specified as post-operative complications. Post-operative complications will be reviewed/monitored at intervals by the DMC.

Serious Adverse Events

SAEs occurring from the time of randomisation until 30 days post cessation of the trial intervention must be recorded on the SAE reporting form in the participant's CRF and emailed to VITAL team (VITAL@warwick.ac.uk) and WCTU (WCTUQA@warwick.ac.uk) within 24 hours of the research staff becoming aware of them.

SAE's Exempt form reporting

All SAEs that fall between the defined timelines above should be reported, however there are some exemptions to this. Appendix A of the protocol lists expected post-operative complications that do not need to be reported as SAE's to WCTU because they are recorded in the CRF as an outcome at day 30 and are anticipated as a result of the population being studied.

Assessment of SAE's

For each **SAE** the following information will be collected from the investigator site:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)

- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to intervention), in the opinion of the investigator (Table 2)

Once received, an independent causality assessment will be undertaken by the CI or delegate or independent clinical reviewer. For any SAEs which are suspected to be caused by the trial intervention by either the CI or site clinician, expectedness will be confirmed by the CI or a delegate at WCTU. SAEs that are deemed to be unexpected and related to the trial will be notified to the Research Ethics Committee (REC) within the relevant deadline. All such events will be reported to the Sponsor, Trial Steering Committee and Data Monitoring Committee at their next meetings. All participants experiencing SAEs will be followed-up until the event has been resolved, unlikely to change, or a final outcome has been reached as per protocol until the end of the trial.

Table 3 **Relationship of SAEs to trial intervention**

Relationship to trial intervention	**Description**
Unrelated	There is no evidence of any causal relationship.
Unlikely to be related	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial intervention or device). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible relationship	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial intervention or device). However, the

	influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable relationship	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

4.3 Responsibilities

Principal Investigator (PI)/delegate

1. Checking for SAEs
2. Using medical judgement in assigning seriousness and causality
3. Ensuring that all SAEs are recorded and reported to the delegate of the Sponsor (WCTU) within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with WCTU if a record of receipt is not received within two working days of initial reporting.
4. Ensuring that SAEs are recorded and reported to WCTU in line with the requirements of the protocol.

Chief Investigator (CI) / delegate or independent clinical reviewer

1. Clinical oversight of the safety of participants participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning causality review of any specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
3. Production and submission of annual reports to the relevant REC.

Sponsor (this will be delegated to WCTU):

1. Central data collection and verification of post-operative complications and SAEs, according to the trial protocol.
2. Expectedness assessment of related SAEs
3. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.

4. Reporting safety information to the independent oversight committees identified for the trial (Data Monitoring Committee (DMC) and / or Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
5. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
6. Notifying Investigators of related and unexpected SAEs that occur within the trial.

Trial Steering Committee (TSC)

In accordance with the Trial Terms of Reference for the TSC, periodically reviewing safety data, blind to the randomised arm, and liaising with the DMC regarding safety issues.

Data Monitoring Committee (DMC)

In accordance with the Trial Terms of Reference for the DMC, periodically reviewing safety data, split by randomised arm, to determine patterns and trends of events, identifying safety issues which would not be apparent on an individual case basis.

4.4 Notification of deaths

Death is collected as a trial outcome. No separate reporting of death is required, unless as an event outcome during SAE reporting. Recruiting centres will be asked to report all deaths that occur during the SAE reporting timeframe (30 days post-surgery) via SAE reporting and by completing and returning a notification of death form to the VITAL team at WCTU. Deaths that occur after 30 days post-surgery are not SAEs and recruiting centres will be asked to complete and return a notification of death form only.

4.5 Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately, and in any event no later than three days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures. Any urgent safety measures taken will be disseminated immediately to all participating sites by email, with a requirement for sites to confirm receipt of the communication within 24 hours.

5. DATA MANAGEMENT

Personal data collected during the trial will be handled and stored in accordance with the 2018 Data Protection Act. Patients will be identified using unique trial number only and no data which identifies participants by name will be shared with nor held at Warwick CTU.

5.1 Data collection and management

We will use the standard CTU trial web-based application for data management. Participant data (including case report forms) will be collected in accordance with the protocol from PQIP database. Clinical data will be collected during the hospital stay up to 30 days after randomisation. Baseline characteristics collected include participant demographics, comorbidities, pre-admission function, quality of life, inclusion/exclusion criteria, consent, surgical speciality, expected duration of surgery, time and date of randomisation. Data captured following randomisation will include administered anaesthetic techniques, post-operative complications, participant satisfaction, quality and speed of recovery, accidental awareness, health resource use, health-related quality of life, SAEs, and survival status.

The case report form (CRF) has been developed by the WCTU in conjunction with PQIP and made available to the participating sites as a paper and electronic CRF (eCRF) for ease of data collection; supporting materials will be available to staff. On all trial-specific documents, other than the signed consent form, the participant will be referred to by a unique trial-specific number in any database, not by name. Signed consent forms will be retained at the recruiting site and will not be shared with WCTU. The trial will be conducted in accordance with the current approved protocol, Good Clinical Practice (GCP), relevant data protection regulations, the trial Data Management Plan, and WCTU standard operating procedures (SOPs). A monitoring plan and risk assessment will be devised to protect participant safety and integrity of trial data.

5.2 Database

The VITAL database will be developed by the Programming Team at WCTU and will link by unique identifiers to the PQIP database. All specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff. For further information regarding the PQIP database, please refer to PQIP study information (www.pqip.org.uk).

5.3 Data storage

All essential documentation and trial records will be stored by WCTU in conformance with the applicable regulatory requirements and access to stored information will be restricted to authorised personnel. Any paper data forms will be stored in a lockable filing cabinet in a secure room, to which access is restricted to authorised personnel. Electronic data will be stored in a secure area of the computer with access restricted to staff working on the trial and the WCTU Quality Assurance team. All databases containing identifiable information will be encrypted and password protected. Any data that are transferred out of the secure environment will adhere to WCTU SOPs.

5.4 Data access and quality assurance

All data access will be controlled by individual usernames and passwords, and any changes to data will require the user to enter their username and password as an electronic signature in accordance with regulatory requirements. Staff will have access restricted to the functionality and data that are appropriate for their role in the trial and will not share their log in details.

5.5 Data Shared with Third Parties

Any data transfer would be in accordance with University of Warwick SOPs and require data sharing/processing agreements to be in place.

5.6 Archiving

Trial documentation and data will be archived for at least ten years after completion of the trial. Trial Master File and associated data will be archived by WCTU; trial data generated at sites will be archived according to local policy.

6. STATISTICAL ANALYSIS

6.1 Power and sample size

The total sample size will be **2500 participants over the two intervention arms (1250 per arm)**. The primary endpoint of this trial is number of days alive and at home 30 days after surgery (DAH30).[66] DAH30 is a continuous number between 0 and 30 which reflects, out of the 30 days following surgery, the total number of those days that a participant spends alive and at home. In this definition, home reflects any place other than hospital. This sensitive measure reflects the number of days from surgery to discharge, and also any hospital readmission(s) during that month as well as survival. If a participant dies within those 30 days, their value is set to 0. The secondary endpoints of this trial include number of days alive and at home 90 days after surgery (DAH90) and survival at 90 days after surgery. The population eligible for entry into VITAL is similar to those participants undergoing elective surgery reported by Bell in 2019 with a mean DAH30 of 25 (SD 6.6).[56] Applying the VITAL trial inclusion and exclusion criteria to sample data using hospital episode statistics, we found a mean DAH90 of 72.9 (SD 21.3) and a 90-day mortality rate of 3.8%. We have adopted a conservative estimate of 7.5 for the standard deviation of DAH30 and a conservative estimate of 22 for the standard deviation of DAH90. With a 5% two-sided significance level and 90% power, the randomisation of 2500 participants (1:1) to either TIVA or inhalational anaesthesia would allow detection of a difference of 1 day in DAH30 between treatment arms. This sample size allows for up to 5% loss-to-follow-up. Also, with a 5% two-sided significance level, this 2500 participant sample will allow us to detect a difference in DAH90 between

arms of 3 days with 90% power, or 4 days, with >95% power. For a safety non-inferiority analysis of 90-day mortality, assuming there is truly no difference between modes of anaesthesia (3.8% mortality), a 2500 participant sample would provide 80% power for a one-sided 95% confidence interval to exclude a 1.9% increase in mortality due to TIVA (a relative risk of 1.5). A one-sided 97.5% confidence interval would exclude an increase due to TIVA of 2.2% (a relative risk of 1.6).

6.2 Statistical analysis of efficacy and harms

6.2.1 Statistics and data analysis

A detailed statistical analysis plan (SAP) will be drafted by the trial statistician, which will be finalised and approved by the CI and an independent statistician before the final data analysis.

All statistical analyses will be undertaken on an intention to treat basis where possible to preserve randomisation, avoid bias from exclusions and preserve statistical power. Hence all participants randomised into the trial, regardless of whether they received their randomised intervention, will be analysed according to their randomised group using data collected up to their final follow-up in the trial (6 month time point, or the last timepoint prior to their withdrawal or loss to follow-up). Patients not receiving surgery or withdrawing consent for follow-up prior to surgery will not be included in relevant denominators.

For the primary outcome of DAH30, each randomised treatment arm's point estimate (and 95% confidence interval) will be reported. In addition, DAH30 will be compared across randomised treatment arms using independent samples t-tests, or Wilcoxon rank sum tests depending on the distribution of the data.

The secondary outcome of DAH90 will be analysed as per the DAH30 techniques. Rates of mortality and major post-operative complications will be assessed across randomised arms using chi-squared tests, with logistic regression used to adjust for stratification variables.

Quality of recovery, participant satisfaction and accidental awareness will be scored using appropriate manuals.

The four stratification factors used at randomisation define sub-groups of interest.

- Surgical speciality* (intrabdominal/musculoskeletal/thoracic/vascular/other)
- Expected duration of surgery (<2hours, ≥2hours)*
- Cancer surgery/non-cancer surgery*
- Preoperative frailty (Rockwood Frailty Score*) - Well/Vulnerable/Frail [65]

Pre-specified sub-group analyses will be undertaken using appropriate modelling techniques. These will be determined following examination of the distributions of the collected data but are anticipated to be linear

regression for DAH30 and DAH90, and logistic regression modelling for mortality rates at 90 days. These exploratory sub-group analyses will have lower power than the main whole trial analysis but are hypothesis-generating and results will be scrutinised graphically via forest plots.

6.2.2 Planned recruitment rate

Recruitment will take place in approximately 40 NHS hospitals across the UK (England, Wales, Scotland and Northern Ireland) with a track record of delivery on clinical research, in order to facilitate enrolment of the required number of participants and ensure relevance to the wider NHS. Assuming a sample size of 2500 participants, each site would enrol approximately 70 participants over the planned 36 months duration for recruitment.

6.2.3 Summary of baseline data and flow of participants

Descriptive statistics will be used to summarise the distribution of baseline variables across each of the randomisation arms. Continuous variables will be reported with means and 95% confidence intervals, if normally distributed, or medians and Interquartile Ranges (IQR) otherwise. Categorical variables will be reported using frequencies and percentages.

A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of participants:

- Assessed for eligibility
- Excluded prior to randomisation (and the frequency of each reason for exclusion)
- Randomised
- Allocated to each randomisation arm
- Receiving or not receiving their randomised treatment
- Followed-up at each protocol specified timepoints
- Lost to follow-up at each protocol specified timepoints (and the frequency of each reason for loss to follow-up)

6.3 Health Economic Evaluation

A prospectively planned economic evaluation will be conducted from an NHS and personal social services perspective, according to the recommendations of the NICE reference case.[67] Use of resources during the index admission, where change can be attributed to anaesthesia, will be captured by PQIP. These will include time in surgery and length of stay by level of care. Participants' community contacts, made in connection with their surgery, will be recorded in the first six months. Participants will be encouraged to use an

electronic or paper calendar to help recall this information at follow-up. Healthcare resource use will be costed using most recently available published national reference costs, reflated to the most recent year.[68,69] We will describe reported resource use disaggregated, providing hospital and community usage time horizons. We will simplify resource collection as much as possible, preparing participants to understand the resource information sought and promoting this recording through diaries.

Generic health-related quality-of-life will be assessed at baseline, at discharge, 30 days and at six months using the EQ-5D-5L questionnaire. EQ-5D-5L scores will be converted to health status scores using the UK value set recommended by NICE guidance at the time of analysis.[70,71] Participant level QALY estimates will be estimated as the area-under-the-curve (AUC) of health status scores over time using the trapezoidal rule. Baseline EQ-5D-5L will be included to minimise bias in the QALY calculation, and to adjust subsequent analyses.[72,73] Whilst a greater number of observations would undoubtedly be desirable, the measurement schedule is necessarily pragmatic within the design of the trial. Varying time to discharge may possibly be a proxy for achieving an adequate quality-of-life. Longer hospital stay increases the contribution of the hospital period to the overall AUC and decreases the contribution of the post-discharge period, as both are time-weighted, hence the (informatively) varying discharge time-point should provide a more accurate QALY estimate than a fixed point, because it better characterises the shape of the AUC. We will perform a sensitivity analysis omitting the discharge point as a check for consistency of findings. We will monitor levels of missingness of resource and outcome data, taking steps to promote quality of reporting.

Within-trial analysis (to six months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness.[74] Mechanisms of missingness of data will be explored and multiple imputation methods will be applied to impute missing data.[75-77] Imputation sets will be used to estimate incremental cost per QALY estimates and confidence intervals. Findings will be analysed and visualised in the cost-effectiveness plane, as cost- effectiveness acceptability curves, net monetary benefit and value of information analysis (EVSI).

Should costs and quality-of-life not converge within six months, more extensive economic modelling using decision-analytic methods may be considered to extend the target population, time horizon and decision context, drawing on best available information from the literature and stakeholder consultations to supplement the trial data. Parameter uncertainty in the decision-analytic model will be explored using probabilistic sensitivity analysis. If longer term decision modelling is to be undertaken, then costs and outcomes will be discounted at 3.5% after the first year of randomisation in line with NICE reference case.[67]

Analyses and modelling will be undertaken in Stata 16 SE (or later release if available). Reporting will follow the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[78]

7. TRIAL ORGANISATION AND OVERSIGHT

7.1 Sponsor and governance arrangements

The University of Warwick will sponsor the trial. Sub-contracts delegating responsibilities to research sites will be established using our standard contracting processes with NHS organisations.

7.2 Research ethics approval

All required ethical approval(s) for the trial will be sought using the Integrated Research Application System. The trial will be conducted in accordance with all relevant regulations. Before enrolling participants into the trial, each trial site must ensure that the local conduct of the trial has the agreement of the relevant NHS Trust Research & Development (R&D) department. Sites will not be permitted to enrol participants into the trial until all required agreements are in place.

Annual reports will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended. The REC will be notified of the end of the trial (whether at planned time or prematurely). The CI will submit a final report to the required authorities with the results, including any publications within one year of the end of the trial.

High quality peer review of this protocol will be provided by the Department of Health and Social Care and the NIHR Health Technology Assessment Board and University of Warwick Sponsorship Committee.

7.3 Trial registration

The trial is registered in advance of recruitment commencing, on the ISRCTN database (https://www.isrctn.com/).

Registration confirmed: ISRCTN62903453

7.4 Notification of serious breaches to GCP and/or trial protocol

Trial protocol deviation and violations

Deviations from clinical trial protocols and GCP occur commonly in clinical studies. The majority of these instances are technical deviations that do not result in harm to the trial subjects or significantly affect the scientific value of the reported results of the trial. Violation is a failure to comply with or variance from GCP and/or the final approved protocol. This results from error, fraud or misconduct. These cases should be documented in the protocol deviation and violation section of the case report form for the trial and

appropriate corrective and preventative actions taken. Deviations will be included and considered when the clinical trial report is produced, as they may have an impact on the analysis of the data.

Serious breach

A "serious breach" is a breach which is likely to effect to a significant degree –

a. the safety or physical or mental integrity of the subjects of the trial; or
b. the scientific value of the trial

The sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase, and will notify the REC in writing of any serious breach of

a. the conditions and principles of GCP in connection with that trial; or
b. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach

7.5 Indemnity

NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS bodies carry this risk themselves or spread it through the Clinical Negligence Scheme for Trusts, which provides unlimited cover for this risk. The University of Warwick provides indemnity for any harm caused to participants by the design of the research protocol.

7.6 Trial timetable and milestones

These milestones are estimated and may subject to change.

	Y1	Y2				Y3				Y4				Y5				Y6	
Task	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2
Development of Protocol																			
Staff recruitment																			
Ethical Approval																			
Oversight Group Setup																			
Collaboration Agreements																			
Pilot Study																			
Site Staff training																			
Recruit participants																			
Review of Pilot Study																			
Recruitment – Main Phase																			
Recruit Participants																			
Follow-up																			
Collection of Participant Follow-up data																			
NHS Digital and equivalent NHS data linkage																			
Analysis																			
Clinical Analysis																			
Health Economics Analysis																			
Final Oversight Meetings																			
Final report to funders																			

7.7 Administration

The trial is managed by a multi-disciplinary team. Trial Management will be based at WCTU, University of Warwick. All day-to-day management of the trial will be the responsibility of the CI, with tasks delegated to appropriate members of the trial management team. All clinical management of the trial will be the responsibility of Dr Joyce Yeung and Dr Shaman Jhanji.

The trial management team will assist and facilitate the setting up of centres wishing to collaborate in the trial. In addition, the trial management team will:

- Set up standardised database access for collaborators
- Organise the telephone randomisation service for formal trial entry
- Monitor the collection of data, process data and seek missing data
- Train local staff with regards to data collection remotely
- Ensure the confidentiality and security of all trial forms and data
- Conduct extensive data checking and cleaning
- Organise any interim and main analyses
- Organise Steering Committee, DMC and Collaborators meetings

The trial management team will receive data downloaded from the PQIP database. Upon receipt, data forms will be checked for completeness and entered into a trial-specific dedicated computer programme.

7.8 Trial Management Group (TMG)

The Trial Management Group, consisting of the project staff and co-investigators involved in the day-to-day running of the trial, will meet regularly throughout the project. Significant issues arising from management meetings will be referred to the Trial Steering Committee, Investigators or Funder, as appropriate.

7.9 Trial Steering Committee (TSC)

The trial will be guided by a group of respected and experienced personnel and trialists as well as three 'lay' representatives. The TSC will have an independent Chairperson. Face to face or online meetings will be held at regular intervals determined by need but not less than once a year. Routine business is conducted by email, post or teleconferencing.

The Steering Committee, in the development of this protocol and throughout the trial will take responsibility for:

- Major decisions such as a need to change the protocol for any reason
- Monitoring and supervising the progress of the trial
- Reviewing relevant information from other sources
- Considering recommendations from the DMC
- Informing and advising on all aspects of the trial

The full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members.

7.10 Data Monitoring Committee (DMC)

A DMC will be appointed comprising of two independent clinicians with experience in clinical trials and an independent statistician. One of the independent clinicians will have experience in undertaking clinical trials in emergency or acute care. The roles of the DMC will include: monitoring the data and making recommendations to the TSC on whether there are any ethical or safety reasons why the trial should not continue; advising the TSC regarding the release of data and/or information; considering data emerging from other related studies. It is anticipated that the DMC members will meet once prior to the commencement of the trial to agree the Committee Charter, once at the end of the 6-month pilot, with subsequent meetings throughout the course of the trial.

DMC meetings will also be attended by the Chief Investigator and Trial Manager/Coordinator (for non-confidential parts of the meeting) and the trial statistician(s). The full remit and responsibilities of the DMC will be documented in the Committee Charter which will be signed by all members.

7.11 Essential Documentation

A Trial Master File will be set up according to Warwick University SOP and held securely at the coordinating centre. The coordinating centre will provide electronic Investigator Site Files to all recruiting centres involved in the trial.

7.12 Financial Support

This project is funded by the National Institute for Health Research (NIHR) Health Technology Assessment [HTA] Programme (NIHR130573). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. The trial will be included on the NIHR Portfolio and is eligible for NHS Service Support costs.

8. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

Local monitoring of protocol compliance

In this pragmatic trial, the precise delivery of trial interventions will be at the discretion of the treating clinical team. The delivery of interventions will be recorded on the case report form, including unanticipated crossover between trial arms.

Monitoring

A risk-based proportionate approach outlined in the monitoring plan which will be developed through discussion with the trial sponsor. It is anticipated that monitoring activity will be predominantly central and remote.

Reporting

Protocol deviations or violations (and actions taken to prevent recurrence) will be recorded in the case report form. Serious breaches of the trial protocol or GCP should be immediately reported to the Chief Investigator. The Chief Investigator in consultation with the PI will take whatever immediate action is required to safeguard the wellbeing of participant(s). The Chief Investigator will notify the Sponsor immediately and Ethics committee within 7 days of becoming aware of the serious breach.

9. CO-ENROLMENT

Co-enrolment with other observational studies will be allowed. Co-enrolment with other interventional trials will be reviewed on a case-by-case basis in accordance with national NIHR-supported co-enrolment guidelines.

10. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Our patient partners, Monica Jefford and John Braun are co-investigators who have both recently undergone major surgery. The trial proposal has also been reviewed by the Royal College of Anaesthetists Patient, Carer and Public Involvement and Engagement (PCPIE) Group, who have lent their support to the trial and provided the team with strong support (https://www.niaa-hsrc.org.uk/PCPIE).

Patient research partners will review the VITAL protocol and participant pathways to ensure that trial processes are acceptable to participants and any potential burden is minimised. They will review patient-

facing documents to ensure that they are fit for purpose and refine our consenting procedures. Monica and John will join our regular Trial Management Committee meetings and review participant recruitment progress.

The Trial Steering Committee will include three additional patient partners who will be our independent patient representatives.

11. CONFIDENTIALITY

The University of Warwick is the Sponsor for the trial. The trial is being conducted in full adherence with the principles of the Declaration of Helsinki and MRC Good Clinical Practice principles and guidelines. It also complies with all applicable UK legislation and Warwick Standard Operating Procedures. All data are being stored securely and held in accordance with the Data Protection Act 2018. All identifiable data are pseudonymised and treated as confidential. All CRFs, questionnaires, trial reports and communication regarding the trial will identify the participants by the assigned unique trial identifier and initials only. Participant confidentiality will be maintained at every stage and identifiable information will not be made publicly available to the extent permitted by the applicable laws and regulations. The trial consent process ensures that participants have the choice of whether or not to continue to participate in data collection and are given all relevant information about the trial to make an informed decision. Participants are informed that they are free to withdraw from the trial at any time during any phase without providing a reason and without prejudice, if they so wish.

12. DISSEMINATION AND PUBLICATION

Data arising from this research will be made available to the scientific community in a timely and responsible manner. The main scientific report will be drafted by senior investigators on behalf of VITAL trial group in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org). VITAL Publication and Dissemination Working Party will agree the membership of a Writing Group Committee, which will take primary responsibility for final data analysis and writing of the scientific report. A Publication and Dissemination Plan for VITAL will be written and available in the TMF.

The results of the trial will be shared widely, and participants are able to request a copy of the results through contacting the local trial team. Patient research partners will help the production of a plain English summary of trial results which will be produced to aid patients and the public in understanding the options and differences in anaesthetic techniques and to consider their preferences. Following the conclusion of the trial, summary information will be made available to patients and the public via trial website. A video and/ or

infographic to communicate trial results to the public will be produced with the support of our PPI research partners.

13. REFERENCES

1. Abbott TEF, Fowler AJ, Dobbs TD, Harrison EM, Gillies MA, Pearse RM. Frequency of surgical treatment and related hospital procedures in the UK: a national ecological study using hospital episode statistics. *BJA: British Journal of Anaesthesia.* 2017;119(2):249-257.
2. Pandit JJ, Andrade J, Bogod DG, et al. 5th National Audit Project (NAP5) on accidental awareness during general anaesthesia: summary of main findings and risk factors†‡. *BJA: British Journal of Anaesthesia.* 2014;113(4):549-559.
3. Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents II: inhalation anaesthetic agents. *BJA Education.* 2013;14(3):106-111.
4. Khan KS, Hayes I, Buggy DJ. Pharmacology of anaesthetic agents I: intravenous anaesthetic agents. *BJA Education.* 2013;14(3):100-105.
5. Checketts MR, Alladi R, Ferguson K, et al. Recommendations for standards of monitoring during anaesthesia and recovery 2015: Association of Anaesthetists of Great Britain and Ireland. *Anaesthesia.* 2016;71(1):85-93.
6. Wigmore TJ, Mohammed K, Jhanji S. Long-term Survival for Patients Undergoing Volatile versus IV Anesthesia for Cancer Surgery: A Retrospective Analysis. *Anesthesiology.* 2016;124(1):69-79.
7. Charlesworth M, Swinton F. Anaesthetic gases, climate change, and sustainable practice. *The Lancet Planetary Health.* 2017;1(6):e216-e217.
8. Campbell M, Pierce JMT. Atmospheric science, anaesthesia, and the environment. *BJA Education.* 2014;15(4):173-179.
9. Landoni G, Lomivorotov VV, Nigro Neto C, et al. Volatile Anesthetics versus Total Intravenous Anesthesia for Cardiac Surgery. 2019;380(13):1214-1225.
10. Chau PL. New insights into the molecular mechanisms of general anaesthetics. *British journal of pharmacology.* 2010;161(2):288-307.
11. Franks NP. Molecular targets underlying general anaesthesia. *British journal of pharmacology.* 2006;147 Suppl 1:S72-81.
12. Tang P, Eckenhoff R. Recent progress on the molecular pharmacology of propofol. *F1000Research.* 2018;7:123.
13. O'Gara B, Talmor D. Lung protective properties of the volatile anesthetics. *Intensive care medicine.* 2016;42(9):1487-1489.
14. Schilling T, M.D., Ph.D., D.E.A.A., Kozian A, M.D., Ph.D., Senturk M, M.D., et al. Effects of Volatile and Intravenous Anesthesia on the Alveolar and Systemic Inflammatory Response in Thoracic Surgical Patients. *Anesthesiology: The Journal of the American Society of Anesthesiologists.* 2011;115(1):65-74.
15. Tanaka K, Ludwig LM, Kersten JR, Pagel PS, Warltier DC. Mechanisms of cardioprotection by volatile anesthetics. *Anesthesiology.* 2004;100(3):707-721.
16. Landoni G, Fochi O, Bignami E, et al. Cardiac protection by volatile anesthetics in non-cardiac surgery? A meta-analysis of randomized controlled studies on clinically relevant endpoints. *HSR Proc Intensive Care Cardiovasc Anesth.* 2009;1(4):34-43.
17. Errando CL, Sigl JC, Robles M, et al. Awareness with recall during general anaesthesia: a prospective observational evaluation of 4001 patients. *BJA: British Journal of Anaesthesia.* 2008;101(2):178-185.
18. Sandin RH, Enlund G, Samuelsson P, Lennmarken C. Awareness during anaesthesia: a prospective case study. *Lancet (London, England).* 2000;355(9205):707-711.

19. Nimmo AF, Absalom AR, Bagshaw O, et al. Guidelines for the safe practice of total intravenous anaesthesia (TIVA): Joint Guidelines from the Association of Anaesthetists and the Society for Intravenous Anaesthesia. *Anaesthesia.* 2019;74(2):211-224.
20. Pandit JJ, Cook TM, Jonker WR, O'Sullivan E. A national survey of anaesthetists (NAP5 Baseline) to estimate an annual incidence of accidental awareness during general anaesthesia in the UK[†]. *British journal of anaesthesia.* 2013;110(4):501-509.
21. Avidan MS, Myles PS. Auditing the national audit projects: impact and implementation. *British journal of anaesthesia.* 2018;121(1):107-111.
22. Vollmer MK, Rhee TS, Rigby M, et al. Modern inhalation anesthetics: Potent greenhouse gases in the global atmosphere. *Geophysical Research Letters.* 2015;42(5):1606-1611.
23. SDU. Carbon Footprint from Anaesthetic gas use. 2013.
24. Sherman J, Le C, Lamers V, Eckelman M. Life Cycle Greenhouse Gas Emissions of Anesthetic Drugs. 2012;114(5):1086-1090.
25. Enlund M, Berglund A, Andreasson K, Cicek C, Enlund A, Bergkvist L. The choice of anaesthetic--sevoflurane or propofol--and outcome from cancer surgery: a retrospective analysis. *Ups J Med Sci.* 2014;119(3):251-261.
26. Jun I-J, Jo J-Y, Kim J-I, et al. Impact of anesthetic agents on overall and recurrence-free survival in patients undergoing esophageal cancer surgery: A retrospective observational study. *Scientific reports.* 2017;7(1):14020. doi:10.1038/s41598-017-14147-9. Accessed 2017/10//.
27. Wu ZF, Lee MS, Wong CS, et al. Propofol-based Total Intravenous Anesthesia Is Associated with Better Survival Than Desflurane Anesthesia in Colon Cancer Surgery. *Anesthesiology.* 2018;129(5):932-941.
28. Gerster AG. II. On the Surgical Dissemination of Cancer. *Ann Surg.* 1885;2(8):98-109.
29. Murthy SM, Goldschmidt RA, Rao LN, Ammirati M, Buchmann T, Scanlon EF. The influence of surgical trauma on experimental metastasis. 1989;64(10):2035-2044.
30. Krall JA, Reinhardt F, Mercury OA, et al. The systemic response to surgery triggers the outgrowth of distant immune-controlled tumors in mouse models of dormancy. *Science translational medicine.* 2018;10(436).
31. Hiller JG, Perry NJ, Poulogiannis G, Riedel B, Sloan EK. Perioperative events influence cancer recurrence risk after surgery. *Nature reviews Clinical oncology.* 2018;15(4):205-218.
32. Yang W, Cai J, Zabkiewicz C, Zhang H, Ruge F, Jiang WG. The Effects of Anesthetics on Recurrence and Metastasis of Cancer, and Clinical Implications. *World J Oncol.* 2017;8(3):63-70.
33. Sessler DI, Pei L, Huang Y, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. *Lancet (London, England).* 2019;394(10211):1807-1815.
34. Jin Z, Li R, Liu J, Lin J. Long-term prognosis after cancer surgery with inhalational anesthesia and total intravenous anesthesia: a systematic review and meta-analysis. *International journal of physiology, pathophysiology and pharmacology.* 2019;11(3):83-94.
35. Yap A, Lopez-Olivo MA, Dubowitz J, Hiller J, Riedel B. Anesthetic technique and cancer outcomes: a meta-analysis of total intravenous versus volatile anesthesia. *Can J Anaesth.* 2019;66(5):546-561.
36. Ren SF, Yu H, Guo YQ, Yu H. Inhalation versus intravenous anesthesia for adults undergoing heart valve surgery: a systematic review and meta-analysis. *Minerva anestesiologica.* 2019;85(6):665-675.
37. Chen F, Duan G, Wu Z, Zuo Z, Li H. Comparison of the cerebroprotective effect of inhalation anaesthesia and total intravenous anaesthesia in patients undergoing cardiac surgery with cardiopulmonary bypass: a systematic review and meta-analysis. *BMJ open.* 2017;7(10):e014629.

38. Prabhakar H, Singh GP, Mahajan C, Kapoor I, Kalaivani M, Anand V. Intravenous versus inhalational techniques for rapid emergence from anaesthesia in patients undergoing brain tumour surgery. *Cochrane Database of Systematic Reviews.* 2016(9).
39. Chui J, Mariappan R, Mehta J, Manninen P, Venkatraghavan L. Comparison of propofol and volatile agents for maintenance of anesthesia during elective craniotomy procedures: systematic review and meta-analysis. *Canadian journal of anaesthesia = Journal canadien d'anesthesie.* 2014;61(4):347-356.
40. Bassi A, Milani WR, El Dib R, Matos D. Intravenous versus inhalation anaesthesia for one-lung ventilation. *The Cochrane database of systematic reviews.* 2008(2):Cd006313.
41. Módolo NSP, Módolo MP, Marton MA, et al. Intravenous versus inhalation anaesthesia for one-lung ventilation. *Cochrane Database of Systematic Reviews.* 2013(7).
42. Herling SF, Dreijer B, Wrist Lam G, Thomsen T, Møller AM. Total intravenous anaesthesia versus inhalational anaesthesia for adults undergoing transabdominal robotic assisted laparoscopic surgery. *Cochrane Database of Systematic Reviews.* 2017(4).
43. Scheiermann P, Herzog F, Siebenhofer A, Strametz R, Weberschock T. Intravenous versus inhalational anesthesia for pediatric inpatient surgery - A systematic review and meta-analysis. *J Clin Anesth.* 2018;49:19-25.
44. Ortiz AC, Atallah AN, Matos D, da Silva EM. Intravenous versus inhalational anaesthesia for paediatric outpatient surgery. *The Cochrane database of systematic reviews.* 2014(2):Cd009015.
45. Kumar G, Stendall C, Mistry R, Gurusamy K, Walker D. A comparison of total intravenous anaesthesia using propofol with sevoflurane or desflurane in ambulatory surgery: systematic review and meta-analysis. *Anaesthesia.* 2014;69(10):1138-1150.
46. Tramèr M, Moore A, McQuay H. Propofol anaesthesia and postoperative nausea and vomiting: quantitative systematic review of randomized controlled studies. *BJA: British Journal of Anaesthesia.* 1997;78(3):247-255.
47. Peng K, Liu HY, Wu SR, Liu H, Zhang ZC, Ji FH. Does Propofol Anesthesia Lead to Less Postoperative Pain Compared With Inhalational Anesthesia?: A Systematic Review and Meta-analysis. *Anesth Analg.* 2016;123(4):846-858.
48. Schraag S, Pradelli L, Alsaleh AJO, et al. Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: a systematic review and meta-analysis. *BMC Anesthesiol.* 2018;18(1):162.
49. Miller D, Lewis SR, Pritchard MW, et al. Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery. *Cochrane Database Syst Rev.* 2018;8:Cd012317.
50. Findlay GP, Goodwin APL, Protopapa K, Smith NCE, Mason M, eds. *A review of the perioperative care of surgical patients. A report by the National Confidential Enquiry into Patient Outcome and Death (2011).* . 2011.
51. Boney O, Bell M, Bell N, et al. Identifying research priorities in anaesthesia and perioperative care: final report of the joint National Institute of Academic Anaesthesia/James Lind Alliance Research Priority Setting Partnership. 2015;5(12):e010006.
52. de Vos AJ, Asmus-Szepesi KJ, Bakker TJ, et al. Integrated approach to prevent functional decline in hospitalized elderly: the Prevention and Reactivation Care Program (PReCaP). *BMC geriatrics.* 2012;12:7.
53. Asher RAJ. The dangers of going to bed. *British medical journal.* 1947;2(4536):967-967.
54. Kortebein P, Symons TB, Ferrando A, et al. Functional impact of 10 days of bed rest in healthy older adults. *J Gerontol A Biol Sci Med Sci.* 2008;63(10):1076-1081.
55. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. *J Am Geriatr Soc.* 2009;57(9):1660-1665.

56. Bell M, Eriksson LI, Svensson T, et al. Days at Home after Surgery: An Integrated and Efficient Outcome Measure for Clinical Trials and Quality Assurance. *EClinicalMedicine.* 2019;11:18-26.
57. Moonesinghe SR, Jackson AIR, Boney O, et al. Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine initiative: patient-centred outcomes. *Br J Anaesth.* 2019;123(5):664-670.
58. Rojas-García A, Turner S, Pizzo E, Hudson E, Thomas J, Raine R. Impact and experiences of delayed discharge: A mixed-studies systematic review. *Health Expect.* 2018;21(1):41-56.
59. Stark PA, Myles PS, Burke JA. Development and psychometric evaluation of a postoperative quality of recovery score: the QoR-15. *Anesthesiology.* 2013;118(6):1332-1340.
60. Bauer M, Bohrer H, Aichele G, Bach A, Martin E. Measuring patient satisfaction with anaesthesia: perioperative questionnaire versus standardised face-to-face interview. *Acta anaesthesiologica Scandinavica.* 2001;45(1):65-72.
61. Brice DD, Hetherington RR, Utting JE. A simple study of awareness and dreaming during anaesthesia. *British journal of anaesthesia.* 1970;42(6):535-542.
62. Grocott MPW, Browne JP, Van der Meulen J, et al. The Postoperative Morbidity Survey was validated and used to describe morbidity after major surgery. *Journal of Clinical Epidemiology.* 2007;60(9):919-928.
63. Rabin R, Charro Fd. EQ-SD: a measure of health status from the EuroQol Group. *Annals of Medicine.* 2001;33(5):337-343.
64. Ustün TB, Chatterji S, Kostanjsek N, et al. Developing the World Health Organization Disability Assessment Schedule 2.0. *Bull World Health Organ.* 2010;88(11):815-823.
65. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne.* 2005;173(5):489-495.
66. Jerath A, Austin PC, Wijeysundera DN. Days Alive and Out of Hospital: Validation of a Patient-centered Outcome for Perioperative Medicine. *Anesthesiology.* 2019;131(1):84-93.
67. NICE. Guide to the methods of technology appraisal 2013.
68. Curtis K, Burns A. *Unit Costs of Health and Social Care 2016.* Personal Social Services Research Unit, University of Kent, Canterbury2016.
69. Costs NR.
70. NICE. Position statement on use of the EQ-5D-5L value set for England. 2019.
71. van Hout B, Janssen MF, Feng YS, et al. Interim scoring for the EQ-5D-5L: mapping the EQ-5D-5L to EQ-5D-3L value sets. *Value Health.* 2012;15(5):708-715.
72. Dritsaki M, Achana F, Mason J, Petrou S. Methodological Issues Surrounding the Use of Baseline Health-Related Quality of Life Data to Inform Trial-Based Economic Evaluations of Interventions Within Emergency and Critical Care Settings: A Systematic Literature Review. *Pharmacoeconomics.* 2017;35(5):501-515.
73. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. *Health Econ.* 2005;14(5):487-496.
74. Willan AR, Briggs AH, Hoch JS. Regression methods for covariate adjustment and subgroup analysis for non-censored cost-effectiveness data. *Health Econ.* 2004;13(5):461-475.
75. Sterne JAC, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ.* 2009;338:b2393.
76. Faria R, Gomes M, Epstein D, White IR. A guide to handling missing data in cost-effectiveness analysis conducted within randomised controlled trials. *Pharmacoeconomics.* 2014;32(12):1157-1170.
77. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med.* 2011;30(4):377-399.

78. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement. *Value Health.* 2013;16(2):e1-5.

14. APPENDICES

APPENDIX A: Clinical outcome definitions within 30 days post-surgery (listed alphabetically)

1. Acute Cardiac events

*Myocardial infarction**

Acute myocardial injury with clinical evidence of acute myocardial ischaemia and with detection of an increase or decrease in cardiac Troponin values with at least one value above the 99th percentile Upper Reference Limit and at least one of the following:

(i) Symptoms of myocardial ischaemia
(ii) New ischaemic ECG changes
(iii) Development of pathological Q waves
(iv) Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischaemic aetiology
(v) Identification of a coronary thrombus by angiography or autopsy

*Non-fatal cardiac arrest**

Successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole, or pulseless electrical activity
requiring cardiopulmonary resuscitation, pharmacological therapy, or cardiac defibrillation

*Cardiac death**

Death with a vascular cause and includes deaths after a myocardial infarction, cardiac arrest and cardiac revascularization procedure

*Coronary revascularization**

Cardiac revascularisation procedure including percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery

* *Any of these outcomes will also count as Major adverse cardiac event (MACE)*

Atrial fibrillation

New onset of irregularly irregular heart rate in the absence of P waves lasting at least 30 s or for the duration of the ECG recording (if <30 seconds)

Use of vasopressor/inotropic support by infusion post-surgery

Deep venous thrombosis

Diagnosis of deep venous thrombosis required any one of the following:

(i) A persistent intraluminal filling defect on contrast venography

(ii) Non-compressibility of one or more venous segments on B mode compression ultrasonography

(iii) A clearly defined intraluminal filling defect on contrast enhanced CT

Pulmonary embolism

Diagnosis of pulmonary embolism requires any one of the following:

(i) A high probability ventilation/ perfusion lung scan

(ii) An intraluminal filling defect of segmental or larger artery on a helical CT scan

(iii) An intraluminal filling defect on pulmonary angiography

(iv) A positive diagnostic test for deep venous thrombosis (e.g. positive compression ultrasound) and one of the following:

(a) Non-diagnostic (i.e. low or intermediate probability) ventilation/perfusion lung scan

(b) Non-diagnostic (i.e. subsegmental defects or technically inadequate study) helical CT scan

2. Acute Kidney Injury Stage 3

According to the KIDGO consensus definition of acute kidney injury (2012): Serum Creatinine 3.0 times baseline OR ≥4.0 mg/dl (≥353.6 mmol/l) increase OR Initiation of renal replacement therapy AND/OR Urine Output <0.3ml/kg/hr for ≥ 24 hours OR No urine output ≥ 12 hours

3. Infective complications

Fever

Core body temperature >38.5 more than 24 hours following surgery with two readings within a 12-hour period

Clinical suspicion of infection and antibiotic use other than prophylaxis

Suspected site: Chest/Urinary/Blood/Wound/Other

4. Post-operative Pulmonary complications

*** Any of the outcomes will also count as Post-operative pulmonary complications*

Exclusions: pulmonary embolism, pleural effusion, cardiogenic pulmonary oedema, pneumothorax and bronchospasm.

*Atelectasis***

Diagnosis on computed tomography or chest radiograph

*Pneumonia***

Two or more serial chest radiographs with at least one of the following features (one radiograph is sufficient for patients with no underlying pulmonary or cardiac disease):

a) new or progressive and persistent infiltrate
b) consolidation
c) cavitation

AND at least one of the following:

a) fever (>38°C) with no other recognised cause
b) leucopaenia (< 4 x 109/L) or leucocytosis (>12 x 109/L)
c) for adults >70 years old altered mental status with no other cause

AND at least two of the following:

a) new onset of purulent sputum or change in character of sputum or increased respiratory secretions or increased suctioning requirements
b) new onset or worsening cough or dyspnoea, or tachypnoea
c) rales or bronchial breath sounds
d) worsening gas exchange (hypoxia, increased oxygen requirement, increased ventilator demand)

*Acute respiratory distress syndrome***

According to the Berlin consensus criteria (2012):

a) Within one week of a known clinical insult or new worsening respiratory symptoms
b) AND bilateral opacities on chest imaging, not fully explained by effusions, lobar/lung collapse, or nodules
c) AND respiratory failure not explained by cardiac failure or fluid overload (requires objective assessment e.g. echocardiogram to exclude hydrostatic oedema if no risk factors are present)
d) AND supplemental oxygenation (requires correcting if altitude >1000m):
    - Mild: PaO2:FiO2 26.7-40.0 kPa with PEEP or CPAP ≥ 5cmH2O
    - Moderate: PaO2:FiO2 13.3-26.6 kPa with PEEP ≥ 5cmH2O
    - Severe: PaO2:FiO2 ≤ 13.3 kPa with PEEP ≥ 5cmH2O

*Pulmonary aspiration***

Diagnosis by clear clinical history AND radiological evidence

Severity (Step-COMPAC definitions):

- Mild: therapeutic supplemental oxygen <0.6 FiO2
- Moderate: therapeutic supplemental oxygen <0.6 FiO2, requirement for high-flow nasal oxygen, or both
- Severe: unplanned non-invasive mechanical ventilation, CPAP, or invasive mechanical ventilation requiring tracheal intubation

6. Stroke

Cerebral infarction or intracerebral haemorrhage on computed tomography or magnetic resonance imaging scan, or new neurological signs (paralysis, weakness, or speech difficulties) lasting >24 hours or leading to earlier death.

APPENDIX B. Grading severity of complications

Clavien-Dindo scale grading

I. Any deviation from the normal postoperative course without the need for pharmacological, surgical, endoscopic or radiological intervention. Anti-emetics, anti-pyretics, diuretics, electrolytes or physiotherapy are not considered a deviation from the normal postoperative course.

II. Requires pharmacological treatment with drugs (including blood transfusion or total parenteral nutrition) other than those excluded from grade I.

III. Requires surgical, endoscopic or radiological intervention.

IV. Life-threatening complication requiring critical care admission

V. Death

APPENDIX C: Definitions of Accidental Awareness under General Anaesthesia

Certain / Probable	A report of AAGA where the detail of the patient story was judged consistent with AAGA, especially where supported by case notes or where report detail was verified independently
Possible	A report of AAGA in which details were judged to be consistent with AAGA or the circumstances might have reasonably led to AAGA, but otherwise the report lacked a degree of verifiability or detail. Where the panel was uncertain whether a report described AAGA, the case was more likely to be classified as possible rather than excluded.
Un-assessable	A report where there was simply too little detail submitted to make any classification possible
Unlikely	Details of the patient story were deemed unlikely