SINFONIA

Sugammadex for preventIoN oF pOst-operative pulmoNary complIcAtions

PROTOCOL

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This protocol has regard for current HRA guidance and content and was prepared in accordance with the SPIRIT statement (2013).

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I. TRIAL SUMMARY

Trial Title	Sugammadex for prevention of post-operative pulmonary complications	
Internal ref. number (or short title)	SINFONIA	
Clinical Phase	Phase 3	
Trial Design	Randomised clinical trial with embedded observational study	
Trial Participants	Patients aged ≥50 years old undergoing elective or emergency major abdominal or non-cardiac thoracic surgery planned to receive neuromuscular blockade with rocuronium or vecuronium with reversal at the end of surgery.	
Exclusions	1. Known allergy to sugammadex, neostigmine or glycopyrrolate 2. Lack of written informed consent for trial participation 3. Planned invasive mechanical ventilation before or after surgery 4. Previous participation in SINFONIA trial 5. Clinician refusal	
Planned sample size	2500	
Treatment Duration	Single bolus dose, repeated once if deemed necessary by the treating clinician	
Follow-up Duration	180 days	
Planned Trial Period	Trial setup: 6 months (June 2022-November 2022) Internal pilot: 12 months (December 2022-November 2023) Trial recruitment (including internal pilot): 36 months (December 2022-November 2025) Follow-up: 6 months (Last participant follow up: -May 2026) Analysis and dissemination: 6 months (June 2026-November 2026)	
	Objectives	Outcome Measures
Primary	(1) To determine whether sugammadex is superior to neostigmine after elective or emergency major abdominal or non-cardiac thoracic surgery in terms of days alive and out of hospital at 30 days (DAH30).	• Days alive and out of hospital at 30 days (DAH30)
Secondary	(1) To determine whether sugammadex is superior to neostigmine after elective or emergency major abdominal or non-cardiac thoracic surgery in terms of patient-centred clinical outcomes.	• Post-operative Pulmonary Complications (PPCs) within seven days after surgery • Mortality at 30 and 180 days after surgery • Quality of recovery on the first post-operative day (QoR-15) • Health-related quality of life at 7, 30 and 180 days (EQ-5D-5L) • Allergic reaction within 24 hours after administration of IMP
	(2) To determine the cost effectiveness of sugammadex compared with neostigmine.	• Health resource use during the 180 days after surgery
	(3) To estimate the rate of allergic sensitisation after a single exposure to sugammadex in a sub-group of participants.	• Rate of allergic sensitisation to sugammadex

IMP(s)	Sugammadex 2-4 mg/kg as a single intravenous bolus at the end of surgery. A second dose of sugammadex can be administered if deemed necessary by the treating anaesthetist to a maximum total dose of 8mg/kg.	Neostigmine 30-70mcg/kg as a single intravenous bolus at the end of surgery, with co-administration of glycopyrrolate (eg 200mcg per 1mg Neostigmine). A second dose of Neostigmine / Glycopyrrolate can be administered if deemed necessary by the treating anaesthetist to a maximum total dose of 5mg Neostigmine (or 70mcg/kg, whichever is less).

II. ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
AR	Adverse Reaction
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
DAH30	Days Alive and out of Hospital at 30 days
DMC	Data Monitoring Committee
GCP	Good Clinical Practice
HES	Hospital Episode Statistics
IMP	Investigational Medicinal Product
IQR	Interquartile Range
ISRCTN	International Standard Randomised Controlled Trial Number
IVRS	Interactive Voice Response System
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
NMBA	Neuromuscular Blocking Agent
PI	Principal Investigator
PPC	Post-operative Pulmonary Complications
PQIP	Perioperative Quality Improvement Programme
PSSRU	Personal Social Services Research Unit

QoL	Quality of Life
QoR-15	Quality of Recovery-15
QALY	Quality Adjusted Life Year
RCoA	Royal College of Anaesthetists
REC	Research Ethics Committee
R&D	Research and Development
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAIL	Secure Anonymised Information Linkage
SAP	Statistical Analysis Plan
SINFONIA	Sugammadex for prevention of post-operative pulmonary complications
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WCTU	Warwick Clinical Trials Unit

1. BACKGROUND

1.1. Existing knowledge

I. Epidemiology and impact of post-operative pulmonary complications

Each year, more than 3 million patients receive a general anaesthetic for a surgical procedure in the NHS [1]. Complications after surgery and anaesthesia are common, leading to delayed discharge from hospital, higher risk of death, and poor long-term health and quality of life [2]. Post-operative Pulmonary Complications (PPCs) are the most common complications after surgery, and have a considerable detrimental effect on patient recovery, survival and length of hospital stay after surgery [2-5]. PPCs affect more than 230,000 patients each year in the NHS, and are associated with increased resource use and treatment costs estimated to cost to the NHS at least £280 million per year. Preventing PPCs would lead to substantial cost and efficiency benefits for the NHS. While many risk factors for PPCs relate to the surgical procedure or the patient and are not easily modifiable, the use of Neuro-Muscular Blocking Agents (NMBAs) and their reversal agents as part of general anaesthesia is an important modifiable risk factor[6].

II. Neuromuscular blocking agents and post-operative pulmonary complications

NMBAs are used as part of general anaesthesia for major surgery to paralyse skeletal muscle, including the respiratory muscles, to facilitate endotracheal intubation, invasive ventilation and surgical access. NMBAs have long been recognised as a key risk factor for PPCs [6]. Despite the use of NMBA antagonists to reverse the paralysis at the end of surgery and many safety precautions, residual muscle paralysis still affects one in three patients after surgery [7,8]. This leaves the patient with weak upper airway and respiratory muscles causing aspiration of oro-pharyngeal secretions, reduced hypoxic drive and hypoventilation [9], leading to PPCs including pulmonary atelectasis, pneumonia and respiratory failure [2], which in turn are associated with increased post-operative mortality [4].

III. Reversal of neuromuscular blocking agents (NMBAs)

Anaesthetists choose between two drugs to reverse the effects of NMBAs, the anti-cholinesterase drug neostigmine, and the NMBA binding drug sugammadex. Neostigmine is itself associated with dose-dependent muscle weakness and impaired lung function [10]. Neostigmine also causes severe bradycardia necessitating co-administration of an anti-cholinergic drug such as glycopyrrolate or atropine, which have numerous autonomic side effects. Compared to neostigmine, sugammadex reverses NMBAs more rapidly and reliably, reducing the incidence of residual muscle weakness after surgery [11].

III. Choice of NMBA reversal agent and post-operative pulmonary complications

A Cochrane systematic review of 41 clinical trials of 4206 patients compared the efficacy and safety of sugammadex with neostigmine for NMBA reversal. Sugammadex use was associated with lower rates of post-operative residual paralysis and fewer hypoxia events after surgery [11]. However, the effect of sugammadex on patient-centred outcomes has not been properly investigated. In a propensity-matched study of 45,712 patients undergoing surgery with NMBAs in 12 US hospitals, sugammadex was associated with a reduced risk of pneumonia and respiratory failure (OR 0.70, [95% confidence interval 0.63-0.77]) compared to neostigmine [6]. Several smaller observational studies have also identified an association between sugammadex use and a reduced incidence of PPCs [12-16]. We identified one small single centre randomised trial of 200 patients, in which sugammadex use was associated with a reduction in 30-day hospital readmission rates compared to neostigmine but this trial lacks statistical power and the findings remain unconfirmed [17].

IV. Sugammadex and allergy

Anaphylaxis complicates up to one in 2500 anaesthetics, and is associated with a 10% mortality rate as well as long-term sequelae for survivors [18]. Life-threatening anaphylactic reactions to sugammadex are currently rare in the UK, with only one case among 64,000 doses administered [19]. By contrast, in Japan where sugammadex is used in 95% of anaesthetics, repeat exposure is therefore common and sugammadex has become the commonest cause of perioperative anaphylaxis with an incidence of one in 5,000 administrations [20,21]. If sugammadex becomes the NMBA reversal drug of choice in the NHS, this will likely lead to a significant increase in perioperative anaphylaxis over the next decade [22].

1.2. Hypothesis

We hypothesise that in adults aged 50 years or older, use of sugammadex for reversal of neuromuscular blockade at the end of elective or emergency major abdominal or non-cardiac thoracic surgery will be associated with fewer post-operative pulmonary complications, and thereby a greater number of days alive and out of hospital at 30 days compared with neostigmine.

1.3. Need for a trial

Improving recovery from surgery and preventing postoperative complications is a public health research priority as defined by patients, carers and clinicians through the James Lind Alliance. There is an urgent need to identify effective methods to reduce the incidence of PPCs. The most important anaesthesia-related risk factor for PPCs is the use (and reversal of) NMBAs as part of general anaesthesia. Sugammadex reduces the incidence of residual muscle paralysis due to NMBAs compared to neostigmine, but evidence for its clinical effectiveness remains limited. There is a steady increase in its use in the NHS [19]. At present there is equipoise amongst anaesthetists about the risks and benefits of this drug but this may change given that immediate benefits (faster reversal of NMBA drugs) are readily apparent to anaesthetists while the principal risk (anaphylaxis) may only become evident some years later, on re-exposure. This clinical trial is needed to define the risks and benefits of sugammadex before further change in NHS practice occurs.

1.4. Research ethics considerations

The trial will be conducted in full conformance with the principles of the Declaration of Helsinki and to ICH Good Clinical Practice (GCP) guidelines. It will also comply with all applicable UK legislation and the Standard Operating Procedures (SOPs) of the University of Warwick and the Sponsor (Belfast Health and Social Care Trust). All data will be stored securely and held in accordance with the UK GDPR.

1.5. Assessment & management of risk

As SINFONIA is comparing two drugs which are routinely used in clinical practice, the level of risk above that of standard care is judged to be minimal. Specifically, although the risk of allergic sensitisation is an important consideration to be addressed in this trial, the individual risk to participants from anaphylaxis to a study drug is approximately 1:128,000.

2. TRIAL DESIGN

2.1. Trial setting

The trial will take place in approximately 40 NHS hospital sites (allergic sensitisation sub-study to take place in approximately five of these sites). Potentially eligible participants will be identified through surgical and joint multidisciplinary meetings, pre-operative assessment clinics and/or operating theatre lists at participating hospitals. A full list of participating sites will be available in the Trial Master File.

2.2. Trial summary

SINFONIA is a multi-centre pragmatic randomised trial comparing the clinical and cost effectiveness of two agents for reversal of neuromuscular blockade at the end of anaesthesia for major surgery, sugammadex and neostigmine, with a primary outcome of days alive and out of hospital at 30 days (DAH30).

2.3. Internal pilot (twelve months)

For a twelve-month internal pilot phase, our target recruitment will be 2-3 participants per site per month from the date the first hospital site opens to recruitment. Allowing for a staggered start to opening at least 20 hospital sites, we anticipate 296 participants will be recruited in the first twelve months. On reaching the pre-defined success criteria, the internal pilot will run seamlessly into the main trial.

2.4. Aims and objectives

2.4.1. Primary objective

The primary objective of SINFONIA is to determine whether sugammadex is superior to neostigmine after elective or emergency major abdominal or non-cardiac thoracic surgery in terms of days alive and out of hospital at 30 days (DAH30).

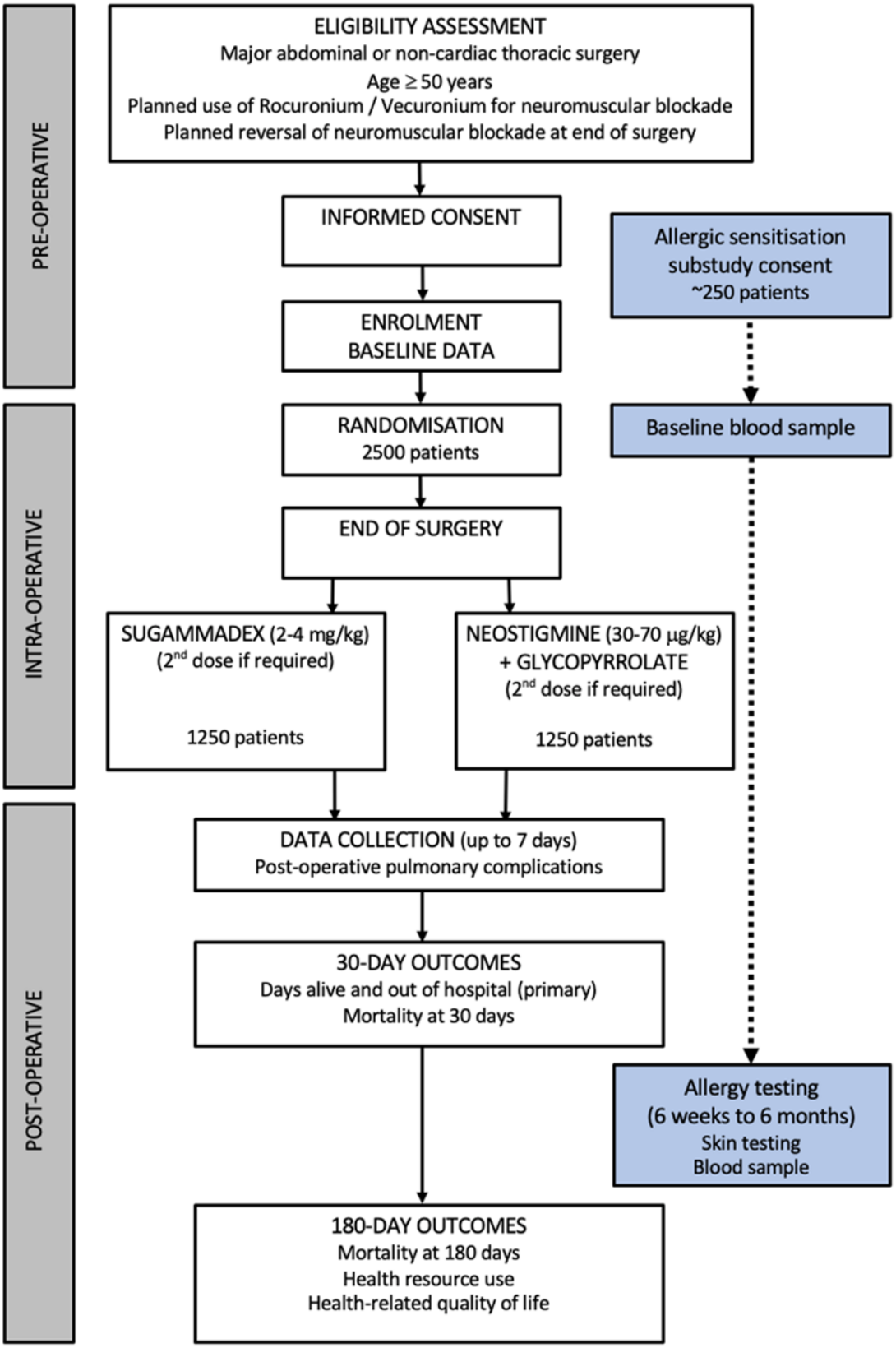
2.4.2. Secondary objective

(a) To determine whether sugammadex is superior to neostigmine in terms of prevention of post-operative pulmonary complications, mortality and other patient-centred outcomes after elective or emergency major abdominal or non-cardiac thoracic surgery.

(b) To determine the cost effectiveness of sugammadex compared with neostigmine.

(c) To estimate the rate of allergic sensitisation after a single exposure to sugammadex.

Figure 1 Trial flow diagram



2.5. Outcome measures

2.5.1. Clinical effectiveness

(a) Days Alive and out of Hospital at 30 days after surgery (DAH30) [24]
(b) Post-operative Pulmonary Complications (PPCs) within seven days after surgery [25]
(c) Mortality at 30 and 180 days after surgery
(d) Quality of Recovery (QoR-15) on the first post-operative day
(e) Health-related quality of life at, 7, 30 and 180 days (EQ-5D-5L)

2.5.2. Safety

(a) Allergic reaction within 24 hours after administration of IMP

2.5.3. Health economics

(a) Health resource use during the 180 days after surgery

2.5.4. Other

(a) Rate of allergic sensitisation to sugammadex (in patients enrolled in the substudy)

2.6. Eligibility criteria

2.6.1. Inclusion criteria

1. Patients presenting for elective or emergency major abdominal or non-cardiac thoracic surgery*
2. Age ≥ 50 years
3. Planned use of rocuronium or vecuronium for neuromuscular blockade
4. Planned reversal of neuromuscular blockade at the end of surgery

*See appendix for examples of eligible major surgical procedures

2.6.2. Exclusion criteria

1. Known allergy to sugammadex, neostigmine or glycopyrrolate
2. Lack of written informed consent for trial participation
3. Planned invasive mechanical ventilation before or after surgery
4. Previous participation in SINFONIA trial
5. Clinician refusal (with reason)

2.7. Participant identification and screening

During the trial recruitment period, hospital research delivery teams will liaise with clinical staff to identify possible trial participants who may be eligible for inclusion. A member of the research delivery team with appropriate knowledge and training will make an initial assessment of eligibility for the potential trial participant. Participant eligibility will then be formally confirmed by the Principal Investigator (PI), or a medically-qualified nominee on the trial delegation log. No additional tests or investigations will be required for assessing eligibility.

2.7.1. Research delivery staff training

Each site will have a named consultant-level investigator who will lead recruitment and act as the Principal Investigator (PI). The local members of research team will be accountable to the PI. The CI and Trial Manager/Coordinator will provide trial-specific training to all sites prior to site initiation and subsequently as required to ensure consistency of practice across all sites. Sites will be provided with access to the secure web-based randomisation system once training is complete, and local site approvals are in place. Site research delivery staff will be listed on the Site Delegation log, detailing the trial activities they are permitted to undertake.

2.7.2. Informed consent

Before surgery, potential participants will be identified and approached by a member of the research team, who is considered part of the direct care team. This approach may be conducted via telephone, online or face-to-face consultations and provides an opportunity for the research team to explain the trial to potential participants in detail. Patient information sheets can be given in person, 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, and further discussion. It is recommended (although not mandated) that the participant is approached at least one day prior to the date of surgery where possible. Written informed consent must be obtained before surgery. It is the responsibility of the Principal Investigator (PI) at each site, or qualified healthcare professionals 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, 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, without their care being affected. 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. Details of patients who are potentially eligible for the trial, but subsequently not recruited, should be recorded (including reason not recruited, but without any personal identifiers) on the electronic patient-screening log provided to sites in the Investigator Site File.

2.8. Enrolment and Randomisation

2.8.1. Enrolment

Following informed consent, the patient will be enrolled in the trial through a simple and secure web-based or Interactive Voice Response System (IVRS) enrolment system that has been established by the programming team at Warwick Clinical Trials Unit. Baseline data, including EQ-5D-5L questionnaire, may be collected prior to randomisation.

2.8.2. Randomisation

Randomisation should be undertaken after induction of anaesthesia where possible, although this is not mandatory. However it is mandatory that randomisation is completed before neostigmine, sugammadex or any neuromuscular blockade reversal drug is administered.

Participants will be randomised on a 1:1 basis to receive either sugammadex or neostigmine. Randomisation will be undertaken through a simple and secure web-based or IVRS randomisation

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

1. Trial hospital site
2. Emergency vs elective surgery
3. Thoracic vs abdominal surgery

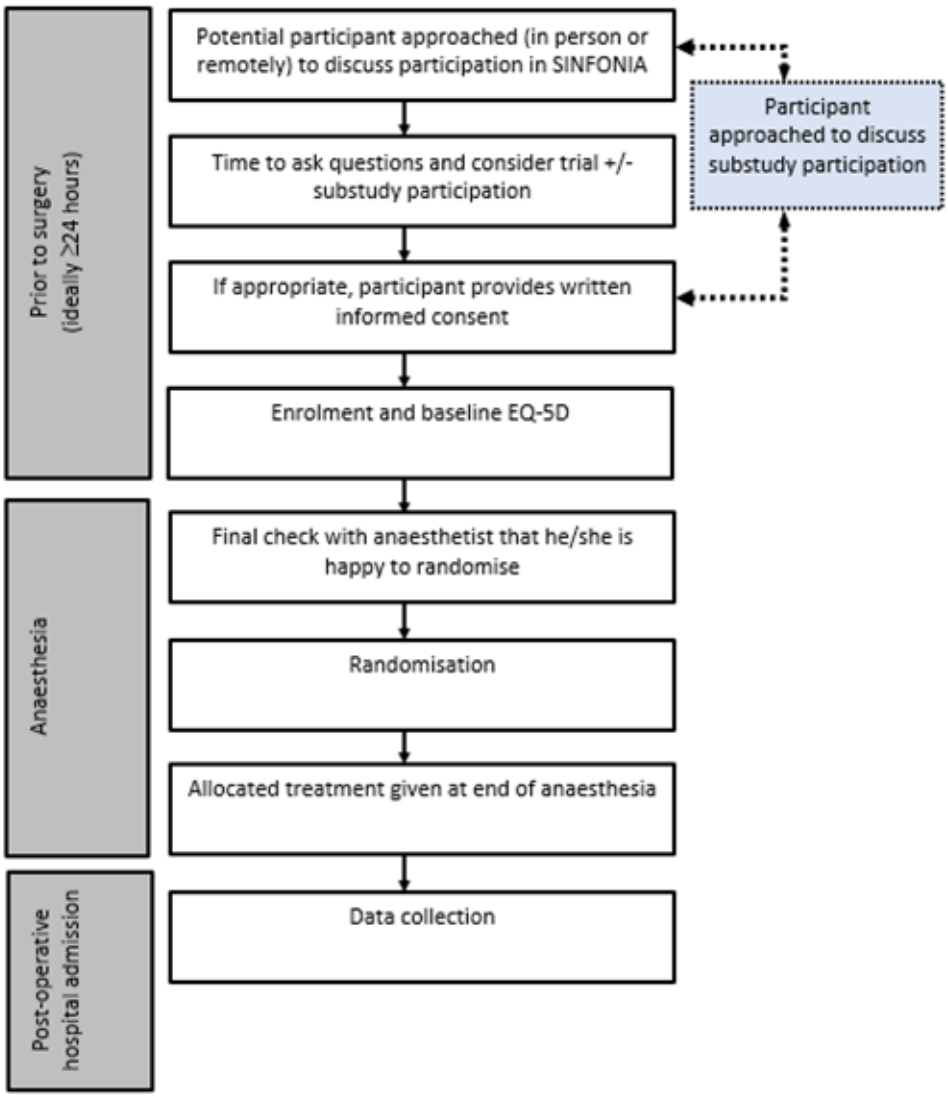
The inclusion of hospital site within this list of factors allows for some instances of predictability of the next treatment allocation. To eliminate this, each patient will have a probability (unspecified here) of being randomised to the opposite trial arm that they would have otherwise received. Full details of the minimisation algorithm will be stored in a confidential document at WCTU. If the web-based or IVRS enrolment/randomisation system is unavailable for technical reasons, an emergency enrolment/randomisation system will be provided by WCTU Monday – Friday, 9am – 5pm. The emergency enrolment/randomisation telephone number will be provided to sites in the Investigator Site Files.

The clinical team will not be blinded to the IMP administered, and this will be recorded in the clinical notes, so there will be no specific unblinding procedure.

2.8.3. Post-randomisation withdrawals, exclusions and moves out of region

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

Figure 2. Consent and Randomisation flow diagram



2.9. Trial treatments and intervention

All patient care outside the SINFONIA trial intervention will be conducted according to routine clinical practice and local guidelines, by experienced anaesthetists. Anaesthetists will be reminded of best practice with regards to neuromuscular monitoring, in keeping with national guidance [26]. More detailed guidance on the trial interventions will be provided to sites during trial-specific training.

2.9.1. Sugammadex

Participants randomised to the sugammadex arm will receive an intravenous bolus of sugammadex (2-4mg/kg) for reversal of neuromuscular blockade around the end of the surgery. Within these

parameters, the precise dose and timing are left to the discretion of the treating anaesthetist. If deemed necessary by the treating anaesthetist, patients allocated to the sugammadex treatment group may be administered a second dose of sugammadex, up to a maximum total dose of 8mg/kg. A third or subsequent dose of sugammadex, or any dose of neostigmine administered, will be outside the trial intervention and will constitute a protocol deviation for monitoring purposes.

2.9.2. Neostigmine

Participants randomised to the neostigmine arm will receive an intravenous bolus of neostigmine (30-70 mcg/kg) for reversal of neuromuscular blockade around the end of surgery, with co-administration of glycopyrrolate at an appropriate dose to prevent muscarinic side effects (for example 200mcg per 1mg of neostigmine). The precise dose and timing are left to the discretion of the treating anaesthetist. If deemed necessary by the treating anaesthetist, patients allocated to the neostigmine treatment group may be administered a second dose, up to a maximum total dose of 5mg neostigmine (or 70mcg/kg, whichever is less). A third or subsequent dose of neostigmine, or any dose of sugammadex administered, will be outside the trial intervention and will constitute a protocol deviation for monitoring purposes.

2.9.3. Study drug identification

This trial has been classified as a Type A CTIMP as the potential risk is no higher than that of standard care. The IMPs will be administered according to usual best practice and will therefore not require any specific storage, labelling or packaging. The IMPs are defined by the active substance only, therefore all authorised brands and concentrations may be used provided they are routinely available for use in the participating hospital concerned.

2.9.4. Other medications

No concomitant medications are prohibited in either treatment arm. Clinical judgment should be applied in the case of any treatments which may interact with either of the study medication, such as toremifine and fusidic acid, which may lower the efficacy of sugammadex; and any medications which may potentiate the cholinergic effects of neostigmine. Since the clinical effects of the IMPs are typically monitored in real time, there is no specific requirement for dose adjustment, but clinicians will be encouraged to exercise their clinical judgment appropriately.

2.9.5. Contraception

Sugammadex may reduce the effectiveness of hormonal contraceptives, similar to the effect of a single missed dose of an oral contraceptive pill. Advice will be given to female participants who are using the oral contraceptive pill, that an alternative method of contraception should be used for 7 days, or that the 'missed dose' advice in the package leaflet of the oral contraceptive they use should be followed.

2.9.6. Pregnancy and lactation

There is no evidence to suggest harmful effects of the IMPs in pregnancy or breastfeeding, and the IMPs are used as part of routine clinical care in pregnant and lactating patients.

2.9.7. Drug storage and dispensing

Drugs will be supplied from routine stock through usual NHS routes via hospital trust pharmacies and will be stored and dispensed according to routine local procedures. Drug accountability will also be managed by trust pharmacies and in line with trust policies.

2.9.8. Compliance and contamination

Since the IMP will be administered intravenously by an anaesthetist, and recorded in the patient medical record, compliance with the assigned trial intervention will be assessed by site research delivery staff review of the medical record and recorded on the case report form (CRF). Non-compliance is defined as failure to administer the assigned treatment within the specified dose range.

2.10. Minimising detection bias and contamination

2.10.1. Minimising outcome reporting bias

Care will be taken not to inform participants of treatment group assignment, except where necessary for patient safety (e.g. allergic reaction). Research delivery staff assessing participant outcomes will be masked to treatment group assignment wherever possible. However, complete blinding of all clinicians and research staff is not feasible. Most patient outcome measures are objective and unlikely to be influenced by knowledge of treatment allocation. Detection of post-operative pulmonary complications is associated with a degree of subjectivity. In order to minimise detection bias, this outcome will be confirmed by a member of the clinical or research team who does not have knowledge of treatment allocation. Research delivery staff assessing participant outcomes will be asked to self-assess their knowledge of the treatment group assignment for each individual patient they follow up (definitely know, possibly know, definitely did not know). During the trial, the Trial Management Group and the Trial Steering Committee will not see outcome results broken down by treatment arm. All data will be collected and cleaned, the database locked, and the statistical analysis plan confirmed before any interim or final data analysis takes place.

2.10.2. Cross over between treatment arms

While we will strongly encourage clinicians to stick to allocated treatments, crossover between treatment arms is possible, for example due to a change in clinical circumstances leading to a perceived advantage of one treatment over the other, or where there is perceived failure of one drug, leading to administration of the second agent. Our primary analyses will be on an intention-to-treat basis, but an additional per-protocol analysis will include only participants who received their allocated treatment only.

2.11. End of trial

The trial will end when 2500 participants have been randomised, the last participant has completed the final follow-up visit, the data cleaning is complete and the database is locked. The trial will be stopped prematurely if:

- Mandated by the Research Ethics Committee (REC)
- Following recommendations from the Data Monitoring Committee (DMC) and Trial Steering Committee (TSC) or Sponsor
- Funding for the trial ceases
- Subject to TSC and funder recommendation, interim pilot progression criteria have not been adequately 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. Where DMC/TSC recommend stopping recruitment only, where possible, follow up data will be collected and cleaned before database lock.

3. METHODS AND ASSESSMENTS

3.1. Schedule of delivery of intervention and data collection

Table 1 Trial assessments

Visit	0	1	2	3	4	5	6
Visit window	Baseline (pre-op)	Day 0 (surgery)	Day 1	Day 7	Day 30	6 weeks to 6 months	180 days
Screening using inclusion / exclusion criteria	X						
Informed consent	X						
Enrolment	X						
Baseline data	X						
Randomisation		X					
Intervention		X					
PPCs				X*			
Duration of hospital stay					X		
Duration of ICU stay (if applicable)					X		
Survival status					X		X+
Hospital readmission					X		
Health resource use					X#		X
Quality of recovery (QoR-15)			X				
Health-related quality of life (EQ-5D-5L)	X			X#	X#		X^
Skin testing for allergic sensitisation~						X	
Blood sampling~		X				X	

*Or until hospital discharge if sooner #Or as close as possible ^+/- 28 days

~Allergic sensitisation substudy participants only

+ Survival check will also be done prior to the dissemination of trial results at the end of trial.

3.2. Follow-up assessments

Day 30 follow up for hospital readmission and mortality will be completed by review of medical records, and if necessary by telephone contact by site research staff with the participant or their General Practitioner. Participants will be contacted by telephone and/or by email at 30 days post-surgery (or as close as possible) and 180 days (or as close as possible) by site research staff to collect data on health resource use based on participant diary and quality of life using EQ-5D-5L.

3.3. Co-enrolment into other trials

Co-enrolment with the Perioperative Quality Improvement Project (PQIP) is encouraged in participating sites. Co-enrolment to other studies will be permitted on a trial-by-trial basis in accordance with national NIHR-supported co-enrolment guidelines.

4. PHARMACOVIGILENCE

4.1. Definitions

4.1.1. Adverse Events (AEs)

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. Adverse Reactions (ARs)

An AR is defined as an untoward and unintended response to either sugammadex or neostigmine.

4.1.3. 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.

4.1.4. Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSARS are SAEs that are considered to be related to the administration of the trial drug and are also unexpected i.e. their nature or severity is not consistent with the Reference Safety Information (RSI).

4.2. Post-operative complications, AEs, SAEs and SUSARs

4.2.1. Assessing and recording of AEs and SAEs

As the study involves a population undergoing surgery and general anaesthesia for major surgery, it is anticipated that many participants will experience events which might be considered AEs or SAEs. Where such events are secondary outcomes or expected features of the perioperative period e.g. wound dehiscence or infection, paralytic ileus, venous thromboembolism, anastomotic leak, myocardial infarction, these will be captured on case report forms but will not be reported as AEs/SAEs. Furthermore, as participants will usually be incapacitated for part of the intervention period, the identification of AEs and SAEs will largely be the responsibility of the clinical team and research teams reviewing patient records. Screening and identification of AEs and SAEs will be based on clinical events (from daily charts and reviews) and review of laboratory and other investigations undertaken as part of routine care. There will be no testing or investigation additional to routine care undertaken for the purpose of detection of AEs or SAEs. All AEs and SAEs will be recorded from the time of IMP administration until 24 hours thereafter (over five half-lives of the IMPs). Where an

AE/SAE is considered relevant to the trial by clinical or research teams, it is the responsibility of the site investigator to review all relevant medical records and to record relevant information in the CRF and on the SAE form if applicable. The investigator will record the intervention group, dose administered, together with the type of event, onset time and date (and relationship with administration), an assessment of severity and causality, and date of resolution, together with any treatment or investigations required and outcome. SAEs will be evaluated for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

4.2.2. Reporting SAEs and SUSARs

SAEs occurring from the time of IMP administration until 24 hours post trial intervention must be notified to the SINFONIA team (SINFONIA@warwick.ac.uk) and WCTU (WCTUQA@warwick.ac.uk) within 24 hours of the research staff becoming aware of them, either by email or by completion of the SAE form in the trial database.

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 PI or delegated medically qualified investigator (see 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, this will be deemed a Serious Adverse Reaction (SAR), and expectedness will be confirmed by the CI or a delegate. For these events, evaluation of expectedness will be made based on knowledge of the reaction and the relevant RSI. SAEs that are deemed to be unexpected and related to the intervention will be deemed SUSARs and will be notified to the REC, MHRA and sponsor 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 until 180 days following surgery.

Any change of condition or other follow-up information should be recorded on an SAE reporting form in the trial database or emailed to the SINFONIA team (SINFONIA@warwick.ac.uk) and WCTU (WCTUQA@warwick.ac.uk) as soon as it is available or at least within 24 hours of the information becoming available. All participants experiencing SAEs will be followed-up until the event has resolved, unlikely to change, or until 180 days following surgery.

For details on SAE reporting in the Allergic Sensitisation sub-study, please refer to section 6.4.4.

4.2.3. AEs Exempt from reporting

As the study involves a population undergoing surgery and general anaesthesia for major surgery, most participants will experience an AE and around one in three participants will experience an SAE. The most frequent examples of anticipated AEs and SAEs include post-operative pain, nausea and vomiting, surgical site infection, post-operative haemorrhage, myocardial infarction, pneumonia. Post-operative complications will not be reported separately as AEs/SAEs unless the PI or medically

qualified designee is concerned that they may be related to the trial treatment group assignment. Data describing post-operative complications (of Clavien-Dindo Grade II severity or above) will be captured in the CRF.

4.2.4. Reference Safety Information

The relevant SPC for each IMP (section 4.8) will be used as the RSI for the trial. Updates to the SPCs will be reviewed and any resultant changes to the RSI will be subject to a substantial amendment prior to implementation.

Table 2. 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 deciding whether an event requires reporting, and for assigning seriousness and causality
3. Ensuring that all events deemed to require reporting as 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 events 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 for assigning causality assessment and expectedness assessment of related SAEs

3. Production and submission of annual reports to the relevant REC.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
6. Preparing the clinical sections and final sign off of the Annual Progress Report (APR).

Sponsor/delegate (WCTU):

1. Central data collection and verification of post-operative complications and SAEs, according to the trial protocol.
2. 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.
3. 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.
4. Expedited reporting of related and unexpected SAEs to the REC within required timelines.
5. Notifying investigators of related and unexpected SAEs that occur within the trial.
6. Updating RSI based on periodic review of SPC

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.

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 regulatory authority and 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 UK GDPR.

5.1. Data collection and management

We will use the standard WCTU trial web-based application for data management. Participant data (including case report forms) will be collected in accordance with the protocol. Clinical data will be collected during the hospital stay up to 30 days after surgery, and thereafter from contact with the patients and their clinical teams up to 180 days. Baseline characteristics to be collected include participant demographics, comorbidities, pre-admission function, quality of life, inclusion/exclusion criteria, consent, surgical speciality, type of surgery, time and date of randomisation. Data captured following randomisation will include administered anaesthetic technique, use of neuromuscular monitoring, PPCs, health resource use, health-related quality of life, SAEs, and survival status. The case report forms (CRF) will be developed by the WCTU and made available to the participating sites as paper and electronic CRFs (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, Signed consent forms will be retained at the recruiting site, they will include an optional consent to collect patients email/postal address for the purpose of dissemination of results at the end of the trial. If the patient has consent to this collection, these details will also be shared with WCTU via the baseline CRF. 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 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 SINFONIA database will be developed by the Programming Team at WCTU. All specifications (i.e. database variables, validation checks, screens) will be agreed between the programmer and appropriate trial staff.

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

The trial statisticians and DMC will have access to the dataset for the analysis of trial outcomes. Once the main analyses have been undertaken, de-identified individual participant data will be available to other investigators subject to approval of data analysis plans and compliance with the University of Warwick SOPs on Data Management and Sharing. Approval of data analysis plans will be the responsibility of the TSC during the lifetime of the trial. Following study completion, the Chief Investigator and WCTU Data Sharing Committee will be jointly responsible for the approval of requests for data from other researchers. Approval will only be provided for proposals which are scientifically sound and have ethical approval. Data sharing agreements will be put in place for any sharing of the trial data. The trial will comply with Data Sharing Policies that may be instituted by the NIHR during the lifetime of the project.

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 for a minimum of 10 years and in accordance with local policy.

6. ALLERGIC SENSITISATION SUB-STUDY (PARTICIPATING SITES ONLY)

6.1. Background

Every anaesthetic carries the risk of a life-threatening allergic reaction to one of the drugs used. In the NHS, this risk is estimated at 1 in every 2500 anaesthetics[18]. For the SINFONIA trial population, one in ten patients die following these reactions, while survivors commonly experience long-term complications such as kidney injury, cognitive impairment and post-traumatic stress disorder[18]. Allergy risks differ between drugs, but in countries where sugammadex has been used widely for many years, this drug has the highest risk of any used in the perioperative period[21]. Serious allergic reactions to sugammadex are currently rare in the UK[19]. However, evidence from Japan suggests that if sugammadex were used routinely in the NHS, this would double the incidence of life- threatening perioperative allergy. In comparison, neostigmine has an allergy risk approaching zero, with only one reported case in the last 20 years in the UK[27]. We can determine the potential rate of sensitisation to this drug following a single exposure, using standard NHS allergy tests. Sensitisation is demonstrated by the presence of IgE antibodies, as detected through skin tests (skin prick and intra-dermal testing) and mast cell activation testing (which requires a blood sample). Sensitisation indicates a significantly increased risk of allergic reactions during future exposure to the drug, but will not provide a precise risk estimate, since many participants with antibodies will not experience a clinical allergy on re-exposure. We can determine the true significance of the sensitisation and the risk of anaphylaxis by administering the drug in small doses in a controlled environment (challenge test). By combining sensitisation information with (a) an understanding of the frequency of re-exposure to sugammadex during future surgery, and (b) a longitudinal survey of sugammadex allergy, we will be able to accurately determine the risk-per-administration of sugammadex in future years as the population prevalence of allergy rises. This risk can then be balanced against any benefits measured in the SINFONIA trial.

6.2. Aim of allergic sensitisation sub-study

To estimate the rate of allergic sensitisation to sugammadex and the future risk of anaphylaxis under anaesthesia.

6.3. Summary of allergic sensitisation sub-study

In SINFONIA trial hospitals with well-established regional allergy services, we will carry out, with participant consent, an observational sub-study to investigate the incidence of allergic sensitisation to sugammadex. This will comprise a baseline blood sample on the day of surgery, with an outpatient clinic visit between 6 weeks and 6 months post-operatively to undertake further blood and skin testing for allergic sensitisation.

6.4. Methods of allergic sensitisation sub-study

6.4.1. Consent and recruitment

Participants in participating SINFONIA allergic sensitisation sub-study sites who are eligible to take part in SINFONIA may be approached for consent to take part in the allergic sensitisation sub-study. Participants will not be required to participate in the sub-study in order to take part in the main trial. Participants in the sub-study will be reimbursed for their travel expenses and compensated for their time in accordance with NIHR guidance.

6.4.2. Baseline blood sampling and processing

Where possible, 10mL of blood will be taken following induction of anaesthesia and prior to the administration of the IMP (either pre- or post-randomisation). Where this is not possible, the blood sample will be taken as close as possible to IMP administration. The samples will be processed in the hospital laboratory, frozen and stored. Samples will be transported in batches to the immunology laboratory at Leeds Teaching Hospitals NHS Trust, at a time of mutual convenience, where mast cell activation testing will be performed. Any samples not used will be disposed of in accordance with local policy and applicable regulations.

6.4.3. Follow-up testing at 6 weeks to 6 months

Following baseline blood sampling, and depending on group allocation, participants will undergo a clinical assessment, comprising review of notes and/or telephone or face to face consultation by an allergy specialist. This assessment will determine suitability for skin testing. Participants will be asked to attend a local drug allergy clinic between 6 weeks and 6 months after their surgery for repeat blood sampling (for mast cell activation) and, if appropriate, a skin test. In line with routine drug allergy skin testing clinics, some medications may be discontinued for a period of one week prior to testing. Where appropriate in the clinical judgment of the allergy specialist, skin testing will be performed at an allergy clinic. This comprises skin prick and intradermal testing on the forearm of both arms, each test 2 cm apart. Immediately prior to this testing, a positive and negative control test will be performed on the forearm using histamine and saline respectively, to ensure that the patient's skin is appropriately reactive. The testing takes around one hour in total and involves minor discomfort from the slight scratching of the skin with each test. Any skin test developing a wheal of 3 mm or greater than the negative control site is usually considered positive but the result of the test is a clinical judgment of the allergy specialist. Systemic reactions to skin testing are rare but can occur, typically involving urticaria and a sensation of itch, although more severe allergic reactions are possible. The testing will be performed by allergy specialists who are trained and experienced in the conduct and management

of skin testing, and who will treat any symptoms which occur in line with local and national guidance. The patient will be contacted between 48 hours and one week following testing to check whether any of the test sites developed localised redness or swelling, which indicates a possible delayed-type allergic reaction. In line with standard drug allergy testing procedure, patients may be offered a drug provocation test, whereby they are given small doses of sugammadex in a carefully monitored setting at the earliest practical opportunity. This is both for future safety of the patient and to understand the specificity of skin testing.

6.4.4. Assessing and recording of sub-study AEs and SAEs

All AEs that relate specifically to sub-study procedures will be recorded from the time of the allergy clinic appointment (sub-study day 0) until 5 days thereafter. Where an AE/SAE is considered relevant to the sub-study by clinical or research teams, it is the responsibility of the site investigator to review all relevant medical records and to record relevant information in the CRF and on the sub-study SAE form if applicable. Where an AE is not related to substudy interventions, it should not be reported. The investigator will record the type of event, onset time and date (and relationship with the allergy testing), an assessment of severity and causality, and date of resolution, together with any treatment or investigations required and outcome.

SAEs will be evaluated for duration and intensity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. SAEs must be notified to the SINFONIA team (SINFONIA@warwick.ac.uk) and WCTU (WCTUQA@warwick.ac.uk) within 24 hours of the research staff becoming aware of them, either by email or by completion of the Allergic sensitisation Sub-study SAE form in the trial database. Any change of condition or other follow-up information should be recorded on an SAE reporting form in the trial database or emailed to the SINFONIA team (SINFONIA@warwick.ac.uk) and WCTU (WCTUQA@warwick.ac.uk) as soon as it is available or at least within 24 hours of the information becoming available. All sub-study participants experiencing SAEs will be followed up until the event has been resolved, is unlikely to change, or for 30 days following the allergy clinic visit.

6.4.5. Statistical analysis of allergic sensitisation sub-study

The results of skin testing, mast cell activation testing, and (if performed) a drug provocation test will be presented using descriptive statistics. A comparison of the risks of different patient groups having 0, 1, 2 or 3 positive results from these tests will be explored. The incidence of positive mast cell activation testing to rocuronium will be compared to current estimates of baseline population sensitisation to rocuronium. This will provide a comparator to understand future sensitisation rates to sugammadex.

6.5. Outcome measures for allergic sensitisation sub-study

1. Positive skin test
2. Positive mast cell activation test
3. Positive sugammadex challenge test

7. STATISTICAL ANALYSIS

7.1. Power and sample size for main trial

We will recruit 2500 participants in total (1250 per trial arm). Based on data from the Secure Anonymised Information Linkage (SAIL) databank in Wales, we expect participants in the neostigmine arm to experience an average DAH30 of 22.4 days (SD 7.4). Assuming a standard deviation of 7.5, with 5% two-sided significance level and 90% power, the randomisation of 2500 participants will allow detection of a one-day difference in DAH30 between trial arms, whilst allowing for 5% loss to follow up. This sample size will also allow us to detect a 3% absolute difference in the incidence of PPCs between trial arms with at least 85% power and 5% two-sided significance, assuming a PPC rate of approximately 7%.

7.2. Statistical analysis of efficacy and harms

7.2.1. Statistics and data analysis

All analyses will be undertaken on an intention to treat basis 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 (six-month time point, or the last timepoint prior to their withdrawal or loss to follow-up). For the primary outcome (DAH30), for each trial arm, point estimates and 95% confidence intervals will be reported, and trial arms compared using independent samples t-tests or Wilcoxon rank sum tests depending on the distribution of the data. PPC and mortality rates will be assessed across trial arms using chi-squared tests. Pre-specified hypothesis-generating sub-group analyses defined by the variables used within the minimisation algorithm will be undertaken using appropriate modelling techniques, decided after examination of the distributions of the collected data but expected to be linear regression for DAH30 and logistic regression for PPC and mortality rates. Results will be scrutinised via forest plots. Warwick Clinical Trials Unit will analyse the data using SAS software (version 9.4 or above) according to a pre-specified statistical analysis plan (SAP) which will be ratified by the trial steering and data monitoring committees.

7.2.2. Planned recruitment rate

Recruitment will take place in approximately 40 NHS hospitals across the UK (England, Wales, Scotland and Northern Ireland) 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 60 participants over the planned 36 months duration for recruitment.

7.2.3. 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)

7.3. Health Economic Evaluation

A prospective economic evaluation will be conducted from an NHS and personal social services perspective using the NICE Reference Case approach. Resource use will include intervention, hospital and community costs (primary care and personal social services) within the 180 days following surgery. Resources will be captured using hospital systems and patient recall (aided by patient diaries). Costs for health and social care resources will be derived by multiplying patient resource use by unit costs from national sources, including Unit Costs of Health and Social Care (PSSRU), NHS Reference Costs and the British National Formulary. The capture strategy for health economic data will be assessed in the internal pilot phase and refined as necessary. Health-related quality of life (EQ-5D-5L) responses will be used to generate quality-adjusted life years (QALYs) using the valuations recommended by NICE and the area-under-the curve method. Within-trial analysis (to six months) using bivariate regression of costs and QALYs will inform a probabilistic assessment of incremental treatment cost-effectiveness. Missingness mechanisms will be explored and multiple imputation methods used if data missingness exceeds 5%, to avoid biases associated with complete case analysis. Imputed analyses will be conducted within Stata using the MI suite of commands. Findings will be presented as incremental cost-effectiveness ratio planes, incremental net monetary benefit, and cost-effectiveness acceptability curves. If the trial shows that sugammadex is not cost-effective then a within trial analysis will be sufficient, as any longer term disbenefit due to sensitisation and subsequent anaphylaxis from sugammadex would reduce cost-effectiveness further. If sugammadex is found (within trial) to be cost-effective then modelling will be required, for which we have expertise and for which further funding will be sought. We have access to NHS health service data (HES) with which to estimate patient survival time from first surgery to further instances of surgery (where these involve anaesthesia with an NMBA) using a Fine and Gray model. We will use these findings, together with trial findings and epidemiological evidence of anaphylaxis, to design and parameterise a probabilistic decision-analytic model. The model will estimate the life-time cost-effectiveness of the choice of NMBA reversal drug.

8. TRIAL ORGANISATION AND OVERSIGHT

8.1. Sponsor and governance arrangements

Belfast Health and Social Care Trust will sponsor the trial. Contracts will be drawn up delegating responsibilities to WCTU and to research sites using standard contracting processes with NHS organisations.

8.2. 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 and the green light to open to recruitment is given.

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. Peer review of this proposal will be provided by the NIHR Health Technology Assessment Programme, Belfast Health and Social Care Trust, and independent members of the SINFONIA trial steering and data monitoring committees.

8.3. Trial registration

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

8.4. 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 affect 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

8.5. 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. Belfast Health and Social Care Trust provides indemnity for any harm caused to participants by the design of the research protocol.

8.6. Administration

The trial is managed by a multi-disciplinary team. All day-to-day management of the trial will be the responsibility of the CI, with tasks delegated to appropriate members of the WCTU team. All clinical management of the trial will be the responsibility of the CI. The WCTU team will assist and facilitate the setting up of sites wishing to collaborate in the trial. In addition, the WCTU team will:

- Set up standardised database access for collaborators

- Organise the web-based 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

8.7. Trial timeline

	2022			2023				2024				2025				2026		
Month	Q2[a]	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3[b]
Protocol development																		
Staff recruitment																		
Regulatory approvals																		
Oversight group setup																		
Collaboration agreements																		
Staff training																		
Internal pilot																		
Review of pilot study																		
Patient recruitment																		
Data collection																		
Allergy sub-study																		
Patient follow-up																		
Data cleaning																		
Data analysis																		
Reporting																		
Final oversight meetings																		

a March-June b July-August

8.8. Trial Management Group (TMG)

The Trial Management Group, consisting of the co-investigators and the project staff 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.

8.9. Trial Steering Committee (TSC)

Trial oversight will be provided by the TSC comprising members if the trial leadership team and a majority of independent clinical researchers with relevant experience as well as patient representatives. The TSC will have an independent Chair. Members of the trial management team will be invited to join TSC members as observers, and to participate in TSC discussions where appropriate. 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 full remit and responsibilities of the TSC will be documented in the Committee Charter which will be signed by all members. 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

8.10. 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 12-month pilot, with subsequent meetings throughout the course of the trial. Open sessions of DMC meetings will be attended as required by the Chief Investigator and Trial Manager/Coordinator to brief DMC members on progress with the trial. The trial statistician will attend both open and closed sessions as required to explain data analyses and answer questions from the DMC. The full remit and responsibilities of the DMC will be documented in the DMC Charter which will be signed by all members.

8.11. Essential documentation

A Trial Master File will be set up according to Warwick University SOP 11 and held securely at the coordinating centre. The coordinating centre will provide electronic Investigator Site Files to all recruiting sites involved in the trial, with guidance on management requirements.

8.12. Financial support

This project is funded by the National Institute for Health and Care Research (NIHR) Health Technology Assessment Programme (Ref NIHR133056). 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.

9. MONITORING AND QUALITY ASSURANCE OF TRIAL PROCEDURES

9.1. 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. This will ensure we evaluate the clinical effectiveness of trial interventions in the way they are used in routine practice. The delivery of interventions will be recorded on the case report form, including unanticipated crossover between trial arms.

9.2. 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. The trial Risk Assessment and Monitoring Plan will detail the risks identified and controls and mitigation measures in place.

9.3. Reporting

Protocol deviations or violations (and actions taken to prevent recurrence) will be recorded in the case report form and captured in the WCTU non-compliance log. 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.

10. CO-ENROLMENT

Co-enrolment with other trials will be reviewed on a case-by-case basis in accordance with national NIHR-supported co-enrolment guidelines and agreed between the CI and CI of the proposed co-enrolling study.

11. PATIENT AND PUBLIC INVOLVEMENT (PPI)

Patient researchers will play an active role in the conduct of the SINFONIA trial. This will include review of the 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. PPI representatives will join our regular Trial Management Committee meetings and review participant recruitment progress. The Trial Steering Committee will include an independent patient representative who is not a member of the SINFONIA team.

12. CONFIDENTIALITY

Belfast Health and Social Care Trust is the Sponsor for the trial. The trial is being conducted in full adherence with the principles of the Declaration of Helsinki and ICH 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 UKGDPR. 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.

13. 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 the SINFONIA trial group in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org). The SINFONIA TSC will agree the membership of a Writing Group Committee, which will take primary responsibility for final data analysis and writing of the scientific report. An inclusive approach to authorship will be used, with trial team members named individually and other participating investigators appropriately acknowledged through group authorship (SINFONIA trial group). A Publication and Dissemination Plan for SINFONIA will be written and available in the TMF. Researchers in recruiting hospitals who make a particularly important contribution to the trial will be invited to join the writing committee. All authors must meet international committee of journal editors criteria to be named authors. The results of the trial will be shared widely. Patient research partners will help the production of a plain English summary of trial results which will be produced to aid participants 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 participants and the public via trial website. Where patients have consented for their email/postal address to be collected, a notification will also be sent to them to advise the results are available. A video and/ or infographic to communicate trial results to the public will be produced with the support of our PPI research partners.

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APPENDIX: EXAMPLES OF ELIGIBLE MAJOR SURGICAL PROCEDURES

Major surgical procedures are expected to last more than 90 minutes, with significant risk of tissue injury and complications, and include the following examples. This list is not exhaustive but simply intended to provide a guide for researchers in assessing participant eligibility.

Gastrointestinal:

Gastrectomy
Oesophagectomy
Fundoplication
Cardiomyotomy
Pancreatectomy
Pancreatic transplant
Bowel resection
Hartmann's procedure
Splenectomy
Adrenalectomy
Hepatic resection
Liver transplant
Component separation repair
Exploratory laparotomy
Repair of perforated ulcer

Gynaecological:

Total abdominal hysterectomy
Cytoreductive surgery
Pelvic exenteration

Thoracic:

Diaphragm repair
Pneumonectomy
VATS/open lobectomy
Pleurectomy
Thymectomy

Urological:

Cystectomy
Nephrectomy
Radical prostatectomy
Renal transplant
Repair of vesico-colic fistula

Vascular:

Aorto-femoral bypass
Axillo-femoral bypass
Abdominal aortic aneurysm repair
Thoracic aortic aneurysm repair

THE FOLLOWING ARE EXAMPLES OF SURGERY WHICH IS NOT CONSIDERED MAJOR AND THEREFORE **NOT ELIGIBLE** FOR INCLUSION:
Laparoscopic cholecystectomy, inguinal hernia repair, appendicectomy, vaginal hysterectomy, diagnostic mediastinoscopy.