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Sugammadex for prevention of postoperative pulmonary complications

Submission date
22/09/2022

Recruitment status
Recruiting

Registration date
21/12/2022

Overall study status
Ongoing

Last Edited
04/04/2025

Condition category
Surgery

[X] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[X] Record updated in last year

Plain English summary of protocol

Background and study aims
The aim is to conduct a large clinical trial comparing two drugs used to prevent lung complications and improve recovery from general anaesthesia in patients undergoing major surgery. General anaesthesia for major surgery requires specialised drugs which temporarily paralyse patients' muscles, called neuromuscular blocking agents (NMBAs). At the end of surgery, the NMBA-induced muscle paralysis is reversed with another drug. Despite careful monitoring, incomplete reversal is common, impacting breathing patterns and predisposing to lung complications such as pneumonia. These complications are common, delay patient recovery and increase the risk of death and long-term health problems. Anaesthetists choose between two drugs to reverse muscle paralysis, neostigmine or a newer drug, sugammadex, which reverses paralysis faster and may help to prevent lung complications after surgery. However, this benefit has not yet been proven and must be weighed against two problems with sugammadex. Firstly, it is more expensive than neostigmine, doubling the drug costs of a general anaesthetic. Secondly, there is concern that allergic reactions may become more common over time with widespread use, although these are extremely rare at present.

Who can participate?
Patients aged 50 years and over undergoing major chest or abdominal surgery

What does the study involve?
Each patient who agrees to participate will be randomly allocated to receive either sugammadex or neostigmine for NMBA reversal after surgery. The researchers will follow patients up to find out if using one drug results in faster recovery or lower risk of death than the other. In a subgroup of patients, the researchers will test to find out whether there are any signs that an allergy to sugammadex has developed and could be a problem in a second operation. This will help them to understand the risks and benefits of each drug.

What are the possible benefits and risks of participating?
Participants will be exposed to one of two drugs to reverse neuromuscular paralysing drugs at the end of surgery. Both drugs are in widespread use in the NHS for this indication, with the decision typically determined by individual anaesthetist preference, and participants would be receiving one or other drug anyway. There is therefore no additional risk to the patient from the

intervention.
The researchers have worked with patient representatives to minimise the burden on participants. Apart from the trial intervention, they aim to keep all other aspects of treatment unchanged from usual care. The researchers will collect only the minimum data required for the study and have outlined elsewhere how this will be kept confidential. They will offer participants a range of contact options for follow-up (e.g. email/telephone/post) in order to minimise the inconvenience involved.
The burden to participants in the allergic sensitisation substudy is greater, as they have a blood sample performed at baseline, and are asked to attend a clinic at 6 weeks to 6 months following surgery for a repeat blood sample, and a skin test if deemed appropriate by an allergy expert. Researchers will be requested, where possible, to take the baseline blood sample from an existing indwelling line (e.g. arterial or central venous line) while the patient is under anaesthesia to minimise any pain or discomfort. The amount of blood being taken (10 ml) is not clinically significant and no adverse effects are anticipated. The blood sample at the follow-up clinic will require venepuncture, but since it will be done by experienced staff and only 10 ml is required, this will be kept to a minimum. The skin test lasts for about 2 hours and involves injections of different concentrations of sugammadex into the skin using very fine needles. Redness, itch and pain are possible, but these are typically minimal and transient and can be treated with antihistamines and paracetamol if required. Patients participating in the allergic sensitisation substudy will be compensated for their time and any transport costs in keeping with NIHR guidance.
In patients undertaking the allergic sensitisation substudy, there is a very small risk of an allergic reaction to the skin test. While this risk is miniscule, it will be mitigated by the test being carried out under the supervision of an allergy expert who is trained in the management of allergic reactions, in a closely monitored environment with all necessary equipment and drugs available to treat an allergic reaction if it were to occur.

Where is the study run from?
University of Warwick (UK)

When is the study starting and how long is it expected to run for?
September 2022 to November 2026

Who is funding the study?
Health Technology Assessment Programme (UK)

Who is the main contact?
SINFONIA@warwick.ac.uk

Study website
https://www.warwick.ac.uk/sinfonia

Contact information

Type(s)
Public

Contact name
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Type(s)
Scientific

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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
1006043

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
21021JS-AS, IRAS 1006043, CPMS 54659

Study information

Scientific Title
Sugammadex for prevention of postoperative pulmonary complications

Acronym
SINFONIA

Study objectives
Primary objective:
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).

Secondary objectives:
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.
2. To determine the cost-effectiveness of sugammadex compared with neostigmine.
3. To estimate the rate of allergic sensitisation after a single exposure to sugammadex in a sub-group of participants.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 20/12/2022, East Midlands - Nottingham 2 Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8169, (0)2071048035, (0)20 71048016; nottingham2.rec@hra.nhs.uk), ref: 22/EM/0231

Study design
Single-blind randomized controlled parallel group trial

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a participant information sheet

Health condition(s) or problem(s) studied
Elective or emergency major abdominal or non-cardiac thoracic surgery

Interventions

Current interventions as of 04/04/2025:
This randomised trial will compare the effectiveness of two drugs for the reversal of neuromuscular blocking agents at the end of anaesthesia to prevent postoperative pulmonary complications and thus recovery after major surgery.

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 randomisation system that has been established by the programming team at Warwick Clinical Trials Unit.

Sugammadex:
Participants randomised to the sugammadex arm should receive an intravenous bolus of sugammadex (2-4 mg/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. The maximum total dose of sugammadex (whether one or two doses are used) should not exceed 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. If the dose of sugammadex administered is outside the specified range, reasons for this will be collected.

Neostigmine:
Participants randomised to the neostigmine arm should 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 200 mcg 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. The maximum total dose of neostigmine (whether one or two doses are used) should not exceed 5mg neostigmine or 70 mcg/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. If the dose of neostigmine administered is outside the specified range, reasons for this will be collected.

Following the surgery patients in both arms will follow this schedule. On Day 1 they will undertake a standard questionnaire to evaluate their recovery. On Day 7 they will be checked for any postoperative pulmonary complications that have occurred within the 7 days since surgery, Day 30 they will be checked for hospital readmission and mortality 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.

Previous interventions:
This randomised trial will compare the effectiveness of two drugs for the reversal of neuromuscular blocking agents at the end of anaesthesia to prevent postoperative pulmonary complications and thus recovery after major surgery.

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 randomisation system that has been established by the programming team at Warwick Clinical Trials Unit.

Sugammadex:
Participants randomised to the sugammadex arm will receive an intravenous bolus of sugammadex (2-4 mg/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 8 mg/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.

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 200 mcg per 1 mg 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 5 mg neostigmine (or 70 mcg/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.

Following the surgery patients in both arms will follow this schedule. On Day 1 they will undertake a standard questionnaire to evaluate their recovery. On Day 7 they will be checked for any postoperative pulmonary complications that have occurred within the 7 days since surgery, Day 30 they will be checked for hospital readmission and mortality 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.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Sugammadex sodium, neostigmine methylsulfate, glycopyrronium bromide, glycopyrronium bromide and neostigmine metilsulfate

Primary outcome measure
Days alive and out of hospital at 30 days following surgery (DAH30), captured via questions on case report form (CRF): ‘Patient still alive at 30 days’ – ‘Since their initial discharge after surgery, has the patient been readmitted to hospital’, if yes space provided to add dates, captured on the day 30 post Op form.

Secondary outcome measures
1. Postoperative Pulmonary Complications (PPCs) within 7 days after surgery, captured via questions on CRF: ‘Post-operative pulmonary complications’ – list of these with Yes/No captured on the day 7 post Op form
2. Mortality at 30 and 180 days after surgery, captured via questions on CRFs:

2.1. Patient still alive at 30 days – captured on day 30 post op form
2.2. Patient still alive at 180 days – captured on day 180 post op form
2.3. If no date of death – captured on day 30/180 post op form
3. Quality of recovery on the first post-operative day, measured using QoR-15 on day 1 post op form
4. Health-related quality of life at 7, 30 and 180 days measured using EQ-5D-5L at baseline, day 7 post op, day 30 post op and day 180 post op
5. Allergic reaction within 24 hours after administration of IMP (clinician defined), captured via question on CRF - In the 24 hours following administration of the IMP, has the patient had an allergic reaction? – collected on day 1 post-op form
6. Health resource use during the 180 days after surgery, captured via questions on CRFs, Details of hospital stay (including critical care admissions and re-admissions) Details of community and outpatient visits, captured on both day 30 and day 180 post-op forms
7. Rate of allergic sensitisation to sugammadex (for the allergic sensitisation sub-study only), captured via a CRF – there will be a Final adjudication panel with overall outcome of allergy testing – captured on the Sub-Study Form with the following options:
7.1. Evidence of clinically relevant sensitisation
7.2. No evidence of clinically relevant sensitisation (all test modalities negative OR a single positive test followed by a negative drug provocation test)
7.3. Low certainty of clinically relevant sensitisation (equivocal results)
7.4. Unable to confirm whether clinically relevant sensitisation present (testing not completed)

Overall study start date
16/09/2022

Completion date
01/11/2026

Eligibility

Key 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

Participant type(s)
Patient

Age group
Adult

Lower age limit
50 Years

Sex
Both

Target number of participants
2500

Key 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)

Date of first enrolment
15/02/2023

Date of final enrolment
01/11/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Aneurin Bevan University Health Board
Lodge Road
Caerleon
Newport
United Kingdom
NP18 3XQ

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast

United Kingdom
BT9 7AB

Study participating centre
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Golden Jubilee National Hospital
Agamemnon Street
Clydebank
United Kingdom
G81 4DY

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
Leeds Teaching Hospitals
Great George Street
Leeds
United Kingdom
LS1 3EX

Study participating centre
North Bristol NHS Trust
Southmead Hospital
Southmead Road
Westbury-on-trym
Bristol
United Kingdom
BS10 5NB

Study participating centre
University Hospital Birmingham
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Royal London Hospital
Whitechapel Road
London
United Kingdom
E1 1FR

Study participating centre
Royal Victoria Hospital
274 Grosvenor Road
Belfast
United Kingdom
BT12 6BA

Study participating centre
The Royal Victoria Infirmary
Queen Victoria Road
Newcastle upon Tyne
United Kingdom
TS1 4LP

Study participating centre
St. Bartholomews Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
Vale University Health Board
Heath Park

Cardiff
United Kingdom
CF14 4XW

Study participating centre
Whipps Cross Hospital
Whipps Cross Road
London
United Kingdom
E11 1NR

Study participating centre
Bronglais General Hospital
Bronglais Hospital
Caradoc Road
Aberystwyth
United Kingdom
SY23 1ER

Study participating centre
Conquest Hospital
The Ridge
St. Leonards-on-sea
United Kingdom
TN37 7RD

Study participating centre
Craigavon Area Hospital
Lurgan Rd
Craigavon
United Kingdom
BT63 5QQ

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
East Surrey Hospital
Canada Avenue
Redhill
United Kingdom
RH1 5RH

Study participating centre
Eastbourne District General Hospital
Kings Drive
Eastbourne
United Kingdom
BN21 2UD

Study participating centre
Forth Valley Royal Hospital
Stirling Road
Larbert
United Kingdom
FK5 4WR

Study participating centre
Good Hope Hospital
Rectory Road
Sutton Coldfield
United Kingdom
B75 7RR

Study participating centre
Heartlands Hospital
Bordesley Green East
Bordesley Green
Birmingham
United Kingdom
B9 5ST

Study participating centre

Hinchingbrooke Hospital
Hinchingbrooke Park
Huntingdon
United Kingdom
PE29 6NT

Study participating centre
Liverpool Women's Hospital Cdc
Liverpool Womens Hospital
Crown Street
Liverpool
United Kingdom
L8 7SS

Study participating centre
Manchester Royal Royal Infirmary
Cobbett House
Oxford Road
Manchester
United Kingdom
M13 9WL

Study participating centre
Newham General Hospital
Glen Road
London
United Kingdom
E13 8SL

Study participating centre
Norfolk and Norwich University Hospital
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
North Manchester General Hospital
Delaunays Road
Crumpsall

Manchester
United Kingdom
M8 5RB

Study participating centre
Peterborough City Hospital
Edith Cavell Campus
Bretton Gate
Bretton
Peterborough
United Kingdom
PE3 9GZ

Study participating centre
Pinderfields Hospital
Aberford Road
Wakefield
United Kingdom
WF1 4DG

Study participating centre
Raigmore Hospital
Old Perth Rd
Inverness
United Kingdom
IV2 3UJ

Study participating centre
Rotherham General Hospital
Moorgate Road
Rotherham
United Kingdom
S60 2UD

Study participating centre
Royal Berkshire Hospital
Royal Berkshire Hospital
London Road
Reading
United Kingdom
RG1 5AN

Study participating centre
Royal Infirmary of Edinburgh at Little France
51 Little France Crescent
Old Dalkeith Road
Edinburgh
Lothian
United Kingdom
EH16 4SA

Study participating centre
Royal Liverpool University Hospital NHS Trust
Royal Liverpool University Hospital
Prescot Street
Liverpool
United Kingdom
L7 8XP

Study participating centre
The Royal Oldham Hospital
Rochdale Road
Oldham
United Kingdom
OL1 2JH

Study participating centre
Scarborough General Hospital
Woodlands Drive
Scarborough
United Kingdom
YO12 6QL

Study participating centre
Solihull Hospital
Lode Lane
Solihull
United Kingdom
B91 2JL

Study participating centre
Sunderland Royal Hospital
Kayll Road
Sunderland
United Kingdom
SR4 7TP

Study participating centre
University Hospital Hairmyres
Eaglesham Road
East Kilbride
United Kingdom
G75 8RG

Study participating centre
Ysbyty Maelor Wrexham
Croesnewydd Road
Wrexham Technology Park
Wrexham
United Kingdom
LL13 7TD

Study participating centre
Wythenshawe Hospital
Southmoor Road
Wythenshawe
Manchester
United Kingdom
M23 9LT

Study participating centre
York Hospital
Wigginton Road
York
United Kingdom
YO31 8HE

Sponsor information

Organisation
Belfast Health and Social Care Trust

Sponsor details
c/o Alison Murphy
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Belfast City Hospital
Lisburn Road
Belfast
Northern Ireland
United Kingdom
BT9 7AB
+44 (0)2476 150963
Alison.Murphy@belfasttrust.hscni.net

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/02tdmfk69

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan

1. Peer-reviewed scientific journals
2. Internal report
3. Conference presentation
4. Publication on website
5. Other publication
6. Submission to regulatory authorities

Intention to publish date
01/11/2027

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date. Any data transfer will be in accordance with the University of Warwick SOPs and will require data sharing/processing agreements to be in place.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 3.0	18/10/2023	05/03/2024	No	No
Protocol file	version 4.0	02/10/2024	04/04/2025	No	No