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STRATIFY: Staging by thoracoscopy in potentially radically treatable non-small cell lung cancer associated with minimal pleural effusion

Submission date
31/01/2019

Recruitment status
No longer recruiting

Registration date
05/04/2019

Overall study status
Completed

Last Edited
24/11/2023

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Early-stage Non-Small Cell Lung Cancer (NSCLC) is potentially curable by 'radical treatment', such as major surgery or a combination of radiotherapy and chemotherapy. However, up to 50% of patients die within 2 years and suffer major side effects. When a rim of fluid surrounds the lung at diagnosis (called Minimal Pleural Effusion (MiniPE)) recurrence risk is high.
In STRATIFY, we are investigating the use of a test called thoracoscopy to detect the spread of cancer to the lining of the lung (pleura). We hope that this study will show that the addition of thoracoscopy to standard investigations for lung cancer with small effusions will help in the detection of the spread of the cancer cells (metastases).

Who can participate?
Male and female patients aged 16 years old and over with a confirmed or suspected diagnosis of stage I-IIIA lung cancer are potentially eligible, subject to all entry criteria being met.

What does the study involve?
Potentially eligible patients will be invited to participate in the screening part of the STRATIFY trial, during which they will be given an ultrasound of the chest to ensure they are suitable to enter the main study. Eligible Patients choosing to take part in the trial will be examined by their trial doctor/nurse and a record of vital signs (blood pressure, temperature, pulse rate) medical history, general well-being and medication taken.
Patients will have the thoracoscopy, either a local anaesthetic thoracoscopy procedure (LAT) or Video Assisted Thoracoscopic surgery (VATS). LAT involves the insertion of a slim telescope into the space between the lung and rib cage. This allows the removal of the small amount of fluid that is there and samples (biopsies) to be taken. These biopsies will identify whether the cancer has spread to the lining outside the lung. LAT is not an operation and does not require a general anaesthetic. It is performed using local anaesthetic to ensure patients are comfortable and very safe. Unlike LAT, VATS is a surgical procedure and is a form of 'keyhole' surgery. VATS is carried out in the operating theatre. It is usually done using a general anaesthetic, which means you will

be asleep for the surgery.
Patients will be requested to provide a sample of pleural fluid during the thoracoscopy, which will be stored and used for future research in lung cancer. This is optional.
Before and after the thoracoscopy, patients will be given a chest X-ray. Patients will be requested to provide one blood sample which will be stored and used for future research in lung cancer. This is optional.
All follow-up continuing after thoracoscopy will be carried out as it would for any other patient receiving standard care. Patients will not be asked to attend further clinics for the purposes of the trial; however, as part of the trial, we will follow progress distantly for 6 months by looking at clinical records to help decide if performing thoracoscopy to look for cancer in the lining of the lung is of overall benefit to patients.

What are the possible benefits and risks of participating?
The possible benefit of taking part in this trial is that patients will receive treatment based on a more accurate staging (description) of the cancer. If pleural spread is discovered, patients will avoid futile and potentially toxic treatments they may otherwise have been exposed to. The trial may also provide information on the treatment of non-small cell lung cancer which could benefit patients in the future.

As well as possible benefits, the trial investigations can also produce side effects.
Both LAT and VATS are safe procedures with most complications being very rare. The most common risk is discomfort. We do however give pain killers prior to, during and after the procedure to minimise any pain cause by LAT/VATS. Other possible complications are all uncommon.
In addition to the possible risks involved with LAT/VATS, patients participating in the trial will need to attend the hospital to have the LAT/VATS performed which may involve an overnight stay in the hospital (up to 3 days stay for VATS) Patients will also have one additional blood test on top of those required pre-LAT/VATS which they would not have had if you were not participating in the trial.

Where is the study run from?
The study will be co-ordinated by the Cancer Research UK Clinical Trials Unit, in Glasgow, and the Lead site will be the Queen Elizabeth University Hospital, Glasgow. The study will be open at 5 further UK sites: Salford Royal Hospital, Guy's And St Thomas', Southmead Hospital, John Radcliffe Hospital, Wythenshawe Hospital, and Kingsmill Hospital.

When is the study starting and how long is it expected to run for?
September 2018 to July 2024

Who is funding the study?
STRATIFY is funded by a grant from the Chief Scientists Office (CSO), Scotland

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
STRATIFY2018

Study information

Scientific Title
Staging by thoracoscopy in potentially radically treatable non-small cell lung cancer associated with minimal pleural effusion

Acronym
STRATIFY

Study objectives
Current study hypothesis as of 18/08/2023:
Lung Cancer is the commonest cause of cancer-related death in the UK. Despite major advances in staging and potentially curative (or radical) treatments (surgery and radiotherapy (RT)), recurrence rates remain high. In patients with Stage I, II and IIIA 2-year mortality is currently 15%, 30% and 50%, respectively. A likely reason for this is radiologically occult metastatic disease and novel staging tools are urgently required. Recent studies have highlighted minimal pleural effusion (Mini-PE) as a marker of particularly high recurrence risk, and excess mortality following radical treatment. Current guidelines do not address the staging of Mini-PE. Previous studies infer occult pleural metastases (OPM) in up to 80% of patients with Mini-PE but agree other factors may be responsible in others, including co-morbidities and reactive effusion.

Precise pleural staging would resolve this uncertainty and avoid futile treatment toxicities in patients with OPM, who unfortunately cannot be cured with radical treatment. It may also reduce the recurrence rate and improve survival following radical treatment by ensuring only patients with curable diseases are referred. Thoracoscopy, either by Local Anaesthetic Thoracoscopy (LAT) or Video Assisted Thoracoscopic Surgery (VATS) is the gold-standard test for pleural malignancy in patients with symptomatic effusion. We will prospectively evaluate thoracoscopy as a pleural staging tool.

Previous study hypothesis:
Lung Cancer is the commonest cause of cancer-related death in the UK. Despite major advances in staging and potentially curative (or radical) treatments (surgery and radiotherapy (RT)), recurrence rates remain high. In patients with Stage I, II and IIIA Non-Small Cell Lung Cancer (NSCLC) 2-year mortality is currently 15%, 30% and 50%, respectively. A likely reason for this is radiologically occult metastatic disease and novel staging tools are urgently required. Recent studies have highlighted minimal pleural effusion (Mini-PE) as a marker of particularly high recurrence risk, and excess mortality following radical treatment. Current guidelines do not address the staging of Mini-PE. Previous studies infer occult pleural metastases (OPM) in up to 80% of patients with Mini-PE but agree other factors may be responsible in others, including co-morbidities and reactive effusion.

Precise pleural staging would resolve this uncertainty and avoid futile treatment toxicities in patients with OPM, who unfortunately cannot be cured with radical treatment. It may also reduce recurrence rate and improve survival following radical treatment by ensuring only patients with curable disease are referred. Local Anaesthetic Thoracoscopy (LAT) is the established gold-standard test for suspected pleural malignancy in patients with symptomatic effusion. We will prospectively evaluate LAT as a pleural staging tool in NSCLC and explore alternative mechanisms for poor outcomes using a range of translational end-points.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 07/08/2019, West of Scotland Research Ethics Service 5 (Ward 11, Dykebar Hospital, Grahamston Road, Paisley , PA2 7DE, United Kingdom; +44 (0)141 314 0213; WoSREC5@ggc.scot.nhs.uk), ref: 19/WS/0093

Study design
Multi-centre observational study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Lung cancer

Interventions

Current interventions as of 18/08/2023:
STRATIFY is a study designed to evaluate the use of thoracoscopy (either LAT or VATS) in the staging and diagnosis of occult pleural metastases (OPM) in stage I-IIIa lung cancer with miniPE. It is designed as a prospective, observational study. This means patients will be recruited to the trial at diagnosis and followed up to determine the prevalence of OPM and the effect diagnosis of these with LAT/VATS has on survival and choice of cancer treatment.
Potentially eligible patients will be identified and assessed by the respiratory physician/site PI coordinating their care or delegated members of the research team. The study can be introduced at earlier clinic visits if eligibility is likely, and this discussion is clinically appropriate. Potential participants will be given sufficient time (in their own judgement) to consider the commitment required to fulfil trial requirements and to decide whether to participate. Where possible, patients will be given up to 48 hours, however, due to the nature of the trial, and since some patients will be attending 'one-stop' clinics, same-day consent is permissible. Patients may choose to defer consent if they required additional time and will be offered a follow-up telephone call with a member of the study team for this purpose. This call will occur no later than 48 hours after Visit 1. In addition, all patients will be made aware that participation is voluntary, and they may withdraw at any time without their standard care being affected. No screening activities related to the trial will be undertaken until informed consent has been obtained. Consent can be obtained face-to-face or remotely. For remote consent, the Patient Information Sheet can be posted or emailed to the patient and then remote consent is sought, via telephone or videoconference. The study must have been adequately explained to the patient and the patient must have had the opportunity to ask questions. This must be fully documented in the patient notes. When the subject attends the first on-site clinical visit, consent must be re-affirmed, and signatures of the subject and PI/designee be obtained on the consent form. Eligibility will be confirmed by a medical practitioner.
Once consented, admission to the sites' local unit will be arranged. Patients will normally be admitted through the medical day unit where baseline study assessment will be completed. At this time the patient will also be consented and prepared for their local anaesthetic thoracoscopy which will happen later that afternoon. This may include updated blood tests should there be no recent ones available. LAT:Local anaesthetic thoracoscopy involves the insertion of a camera through the chest wall in order to visualise the linings of the lung and take tissue samples (biopsies) for further investigation. LAT usually takes about one hour from start to finish.
You will be awake for this procedure but will be given sedation. A further ultrasound will be performed when you are positioned for the LAT to confirm the thoracoscopy insertion site. This site will be marked and local anaesthetic injected to numb the area prior to starting. Any pleural fluid surrounding the lung will be drained and sent for investigation and biopsies will be taken. On completion of the thoracoscopy, a chest drain will be inserted into the insertion site. To create more room to work during the thoracoscopy, air is allowed into the pleural cavity.
This chest drain is therefore inserted to allow this air and any remaining fluid to escape. A post-thoracoscopy CXR is performed to assess the position of this drain. Once all of this air has escaped and the lung has fully reinflated (as determined by a further CXR and drain inspection) this chest drain will be removed. Most commonly this is on the day of or the morning after LAT.
VATSVATS also involves the insertion of a slim telescope into the space between your lung and ribcage. This allows the removal of the small amount of fluid that is there and samples (biopsies) to be taken. These biopsies will tell your doctors whether your cancer has spread to the lining outside the lung. Unlike LAT, VATS is a surgical procedure and is a form of 'keyhole' surgery. VATS is carried out in the operating theatre. It is usually done using a general anaesthetic, which means you will be asleep for the surgery. VATS consists of one or more small incisions. One of these incisions allows insertion of the camera and any others are used for the insertion of other instruments such as those needed to take samples. Any samples of tissue taken will be sent to the laboratory for further testing and will tell your doctors whether your cancer has spread to

the lining outside the lung. Once the operation is finished, the instruments are removed. A chest drain will be inserted at the end of the VATS procedure. This allows your lung to fully re-inflate back to its normal position and will be removed as soon as possible, following a review of a chest x-ray after your VATS. The chest drain is a thin plastic tube that is connected to a drainage bottle. For the time the drain is in you will need to be careful to carry the bottle with you when moving around, e.g. going to the toilet. You will be given painkillers on the ward should you experience any discomfort from the drain being in. The average hospital stay after VATS is three days, but it may be shorter or longer depending on your recovery.
All patients will receive a follow-up appointment around one-week post thoracoscopy to discuss the results of any biopsies taken and the management plan based on these findings. After this, all follow-ups will be decided by the team responsible for your routine care. As part of STRATIFY however your progress in terms of treatments given, evidence of recurrence and survival will be assessed every 2 months for the next 6 months. This will be done distantly and therefore will not involve any further clinical visits out with those planned as part of your routine standard care.

Previous interventions:
STRATIFY is a study designed to evaluate the use of local anaesthetic thoracoscopy (LAT) in the staging and diagnosis of occult pleural metastases (OPM) in stage I-IIIa non-small cell lung cancer with miniPE. It is designed as a prospective, observational study. This means patients will be recruited to the trial at diagnosis and followed up to determine the prevalence of OPM and the effect diagnosis of these with LAT has on survival and choice of cancer treatment.
We will also be recruiting an eligible proportion of patients into an additional sub-study in order to determine how MRI markers compare to LAT in the detection of OPM in such patients.

Potentially eligible patients will be identified and assessed by the respiratory physician/site PI coordinating their care (or delegated members of the research team). Eligibility can be considered before completion of routine staging and formation of a oncology treatment plan. However, formal eligibility assessment must only occur after this process has been concluded, at a formal screening visit (Visit 1, Day 0). The study should only be introduced at earlier clinic visits, if eligibility is likely and this discussion is clinically appropriate. Potential participants will be given sufficient time (in their own judgement) to consider the commitment required to fulfil trial requirements, and to decide whether or not to participate. Where possible, patients will be given up to 24 hours, however due to the nature of the trial, and since some patients will be attending ‘one-stop’ clinics, same-day consent is permissible. Patients may choose to defer consent if they required additional time and will be offered a follow-up telephone call with a member of the study team for this purpose. This call will occur no later than 48 hours after Visit 1. In addition, all patients will be made aware that participation is voluntary and they may withdraw at any time without their standard care being affected. No screening activities related to the trial will be undertaken until informed consent has been obtained. Eligibility will be confirmed by a medical practitioner.

Patients will be recruited from to the MRI sub-study within the main study. Patients will be screened for eligibility and provided with an additional MRI sub-study PIS at Visit 1. Patients will be given sufficient time to consider participation (in their own judgement) and similar support will provided as in the main study, including the offer a follow-up telephone call with a member of the research time within 48 hours. Patients will be made fully aware that participation is voluntary and they can leave the trial at any time without their standard care being affected.

Once consented, admission to the sites's local unit will be arranged. Patients will normally be admitted through the medical day unit where baseline study assessment will be completed. At this time the patient will also be consented and prepared for their local anaesthetic thoracoscopy which will happen later that afternoon. This may include updated blood tests

should there be no recent ones available.
LAT:
Local anaesthetic thoracoscopy involves the insertion of a camera through the chest wall in order to visualise the linings of the lung and take tissue samples (biopsies) for further investigation. LAT usually takes about one hour from start to finish.
You will be awake for this procedure but will be given sedation. A further ultrasound will be performed when you are positioned for the LAT to confirm thoracoscopy insertion site. This site will be marked and local anaesthetic injected to numb the area prior to starting.
Any pleural fluid surrounding the lung will be drained and sent for investigation and biopsies will be taken. On completion of the thoracoscopy, a chest drain will be inserted into the insertion site. To create more room to work during the thoracoscopy, air is allowed into the pleural cavity. This chest drain is therefore inserted to allow this air and any remaining fluid to escape. A post-thoracoscopy CXR is performed to assess position of this drain. Once all of this air has escaped and the lung has fully reinflated (as determined by a further CXR and drain inspection) this chest drain will be removed. Most commonly this is on the day of or the morning after LAT.

MRI Substudy:
Patients will attend the local site's imaging facility. An MRI safety checklist, +/- x-ray of the eye sockets to exclude metal fragments, will be completed by a member of the research imaging team. An MRI scan of the chest will then be performed. This involves lying flat inside the MRI scanner for 40-60 minutes. An injection of dye will be given through a drip during the scan and patients will also be asked to hold their breath for a short period a few times during the scan. This has been shown to be easily managed in the vast majority of patients with MPE in a similar protocol used in previous work within our unit (DIAPHRAGM MRI sub-study).

All patients will receive a follow up appointment around one week post LAT to discuss the results of any biopsies taken and the management plan based on these findings.
After this, all follow up will be decided by the team responsible for your routine care. As part of STRATIFY however your progress in terms of treatments given, evidence of recurrence and survival will be assessed every 2 months for the next 6 months. This will be done distantly and therefore will not involve any further clinical visits out with those planned as part of your routine standard care.

Intervention Type
Procedure/Surgery

Primary outcome(s)
Current primary outcome measure as of 18/08/2023:
The true prevalence of detectable OPM, as defined by the proportion of recruited patients with lung cancer cells in parietal pleural biopsies (pathology) or pleural fluid (cytology) obtained during Thoracoscopy (LAT or VATS)

Previous primary outcome measure:
The true prevalence of detectable OPM, as defined by the proportion of recruited patients with NSCLC cells in parietal pleural biopsies (pathology) or pleural fluid (cytology) obtained during Local Anaesthetic Thoracoscopy, at visit 3

Key secondary outcome(s))
Current secondary outcome measure as of 18/08/2023:
1. Thoracoscopy results, recorded as OPM demonstrated/OPM not demonstrated (via pathology and cytology tests)

2. RFS, defined as the time from completion of lung cancer treatment (surgery, radical radiotherapy or radical chemo-radiotherapy) to documented recurrence of lung cancer or death from any cause. Treatment and Survival data will be collected from a review of clinical notes at the site and recorded in the study electronic CRF
3. OS, defined as the time from lung cancer treatment to death from any cause. Survival data will be collected from a review of clinical notes at the site and recorded in the study electronic CRF
4. LAT/VATS feasibility will be recorded as LAT/VATS complete/LAT/VATS incomplete (specify) /LAT/VATS not performed (specify). This information will be collected from a review of clinical notes at the site and recorded in the study electronic CRF, following the pre-LAT/VATS examinations such as US and x-Ray and the LAT/VATS itself

Previous secondary outcome measure:
1. LAT results, recorded as: OPM demonstrated/OPM not demonstrated (via pathology and cytology tests)
2. RFS, defined as the time from completion of NSCLC treatment (surgery, radical radiotherapy or radical chemo-radiotherapy) to documented recurrence of NSCLC or death from any cause. Treatment and Survival data will be collected from review of clinical notes at site and recorded in the study electronic CRF.
3. OS, defined as the time from NSCLC treatment to death from any cause. Survival data will be collected from review of clinical notes at site and recorded in the study electronic CRF.
4. LAT feasibility will be recorded as LAT complete/LAT incomplete (specify)/LAT not performed (specify). This information will be collected from review of clinical notes at site and recorded in the study electronic CRF, following the pre-LAT examinations such as US and x Ray and the LAT itself

5. MRI Sub-study Exploratory outcome measures:
This information will be collected from review of the relevant imaging clinical records at site :
5.1 Pleural MRI results (Presence or Absence of Pleural MRI-ECE or Pleural Pointillism) relative to LAT results
5.2 Systemic co-morbidity will be assessed using validated MRI end-points for cardiac dysfunction and body composition (including sarcopaenia, via muscle cross-sectional area) and related to LAT results, OS, PFS

Completion date
31/07/2024

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 18/08/2023:
1. Suspected or confirmed stage I-IIIA lung cancer
2. Mini-PE, defined as an ipsilateral pleural effusion, resulting in < 1/3 hemithorax opacification on erect chest radiograph which is either:
2.1. Too small to safely aspirate after US assessment (level 1 operator judgement)
2.2. Cytology-negative after diagnostic aspiration
3. Performance Status 0-2
4. Radical treatment feasible (Surgery, Radical RT or chemo-RT, +/- immunotherapy)) if OPM is excluded by thoracoscopy (local PI judgement)
5. Aged 16 or over
6. Informed written or remote consent
7. Willingness to comply with scheduled visits, study procedures and laboratory tests

Previous participant inclusion criteria:
Eligibility Criteria for the Main Study
1. Stage I-IIIA NSCLC, after completion of routine staging
2. Mini-PE, defined as an ipsilateral pleural effusion, which is ≤ 40 mm in max depth on axial CT scan and either:
2.1 Too small to safely aspirate after US assessment (level 1 operator judgement)
2.2 Cytology-negative after diagnostic aspiration
3. Performance Status 0-2
4. Radical treatment feasible (Surgery, Radical RT or chemo-RT) if OPM excluded by LAT (MDT judgement)
5. Aged 16 or over
6. Informed written consent
7. Willingness to comply with scheduled visits, study procedures and laboratory tests

Eligibility Criteria for the MRI sub-study
1. Registered to the main STRATIFY study
2. Informed written consent
3. Willingness to comply with scheduled visits, and study procedures

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Sex
All

Key exclusion criteria
Current Participant exclusion criteria as of 18/08/2023:
1. Any metastatic disease, including confirmed pleural metastases
2. Any contraindication to the selected thoracoscopy method when LAT is the preferred method:
2.1. Absent lung sliding or extensive fluid loculation on pleural ultrasound (not applicable to VATS) when VATS is the preferred method:
2.2. Insufficient fitness for general anaesthesia (not applicable to LAT)
3. Uncorrectable bleeding disorder (applicable to LAT and VATS)

Previous participant exclusion criteria:
Main study:
1. Any metastatic disease, including confirmed pleural metastases
2. Bilateral pleural effusions
3. Any contraindication to LAT, e.g.:
3.1 Absent lung-sliding on pleural ultrasound
3.2 Uncontrollable cough
3.3 Uncorrectable bleeding disorder

MRI Sub-study Exclusion Criteria
1. Any contraindication to MRI, including but not limited to:
1.1 Claustrophobia, pregnancy
1.2 Metallic foreign body
1.3 Pacemaker/implant
1.4 Allergy to Gadolinium contrast
1.5 eGFR <30 ml/min

Date of first enrolment
01/12/2019

Date of final enrolment
31/10/2023

Locations

Countries of recruitment
United Kingdom

England

Scotland

Study participating centre
NHS Greater Glasgow & Clyde, Queen Elizabeth Iniversity Hospital
1345 Govan Rd
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G51 4TF

Study participating centre
University Hospital of South Manchester NHS Foundation Trust
Wythenshawe Hospital
Southmoor Road
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M23 9LT

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe
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Headley Way
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Study participating centre
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Southmead Road
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BS10 5NB

Study participating centre
Guy's and St Thomas NHS Foundation Trust
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Great Maze Pond
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Study participating centre
Salford Royal NHS Foundation Trust
Stott Lane
Salford
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M6 8HD

Study participating centre
University Hospitals Plymouth NHS Trust
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Derriford Road
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Study participating centre
Kingsmill Hospital
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Sponsor information

Organisation
NHS Greater Glasgow and Clyde

ROR
https://ror.org/05kdz4d87

Funder(s)

Funder type
Government

Funder Name
Chief Scientist Office

Alternative Name(s)
CSO

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date

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?

Protocol article		23/11/2023	24/11/2023	Yes	No
HRA research summary			28/06/2023	No	No
Protocol file	version 5.0	16/11/2022	18/08/2023	No	No