STRATIFY

Staging by **T**horacoscopy in potentially **Ra**dically **T**reatable Lung Cancer associated w**i**th Minimal Pleural E**f**fusion

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This trial will be performed according to the UK Policy Framework for Health and Social Care Research and World Medical Association Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended)

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SUMMARY

SUMMARY		
Title	**STRATIFY:** Staging by Thoracoscopy in potentially Radically Treatable Lung Cancer associated with Minimal Pleural Effusion	
Background:	Lung cancer is the commonest cause of cancer-related death in the UK. Despite major advances in staging radical treatments (surgery and radiotherapy (RT)), recurrence rates remain high. In patients with Stage I, II and III Lung Cancer 2-year mortality is currently 15%, 30% [1] and 50%[2], respectively. A likely reason for this is radiologically occult metastatic disease and better 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 [3, 4]. 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 [4,5,11], 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 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. 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 [9, 12]. We will prospectively evaluate thoracoscopy as a pleural staging tool	
Study Design	Multi-centre observational study	
Study Population	50 patients with suspected or confirmed stage I-III lung cancer and Mini-PE	
	Trial Objectives	**Associated Endpoint(s)**
Primary	To determine the prevalence of detectable OPM in patients with suspected or confirmed Stage I-III lung cancer and Mini-PE	The prevalence of detectable OPM, as defined by the by the proportion of patients with lung cancer affecting the parietal pleura, based on thoracoscopic sampling (LAT or VATS).
Secondary	To determine the impact of thoracoscopy results on recurrence free and overall survival (RFS and OS) in patients with stage I-III lung cancer and Mini-PE	• Thoracoscopy results, recorded as: OPM demonstrated/not demonstrated • Recurrence free survival (RFS), defined as the time from completion of lung cancer treatment to recurrence or death from any cause • Overall survival (OS), calculated from thoracoscopy to death from any cause

<table>
<tr><th colspan="3">SUMMARY</th></tr>
<tr><td></td><td>To determine whether staging thoracoscopy is feasible and safe in patients with stage I-III lung cancer and Mini-PE</td><td>• LAT feasibility will be recorded as LAT complete/incomplete/not feasible
• VATS feasibility will be recorded as complete /incomplete/not performed
• Safety will be defined by Adverse Event (AE) and Serious AE (SAE) rates</td></tr>
<tr><td></td><td>To determine the impact of thoracoscopy results on oncological treatment plans in patients with stage I-III lung cancer and Mini-PE</td><td>• Thoracoscopy results, recorded as: OPM demonstrated/not demonstrated
• The treatment plan prior to registration
• The treatment plan following LAT/VATS</td></tr>
<tr><td>Exploratory</td><td>To determine the diagnostic performance of blood/pleural fluid biomarkers for OPM and/or adverse outcomes in subsequent studies</td><td>Venous blood and pleural fluid samples will be collected but not analysed in this study</td></tr>
<tr><td>Eligibility Criteria</td><td colspan="2">MAIN STUDY</td></tr>
<tr><td></td><td>Inclusion Criteria:
• Suspected or confirmed stage I-III lung cancer *
• Mini-PE, defined as an ipsilateral pleural effusion, which is < 1/3 hemithorax opacification on erect chest radiograph and either:
o too small to safely aspirate after ultrasound (US) assessment (level 1 operator)
o cytology-negative after diagnostic aspiration
• Performance Status 0-2
• Radical treatment feasible (Surgery, Radical RT or chemo-RT+/- immunotherapy) if OPM excluded by thoracoscopy
• ≥16 years of age
• Informed written or remote consent
*Based on CT. PET-CT can be post-registration/thoracoscopy if this is optimal pathway</td><td>Exclusion Criteria:
o Any metastatic disease, including confirmed pleural metastases
o Any contraindication to the selected thoracoscopy method, including but not limited to:
When LAT is the preferred method:
o absent lung-sliding or extensive loculation on pleural ultrasound (not applicable to VATS)

When VATS is the preferred method:
o insufficient fitness for GA (not applicable to LAT)
o uncorrectable bleeding disorder (applicable to LAT and VATS)

<u>NB</u>: Patients with bilateral pleural effusions are not excluded but there should be sufficient suspicion of OPM to justify thoracoscopy (in the opinion of the PI), e.g., asymmetrical collections with a larger effusion ipsilateral to the primary disease</td></tr>
<tr><td>Study Period</td><td colspan="2">Study duration: 36 months
Recruitment: 18 months
Per patient study duration: 6.5 months</td></tr>
</table>

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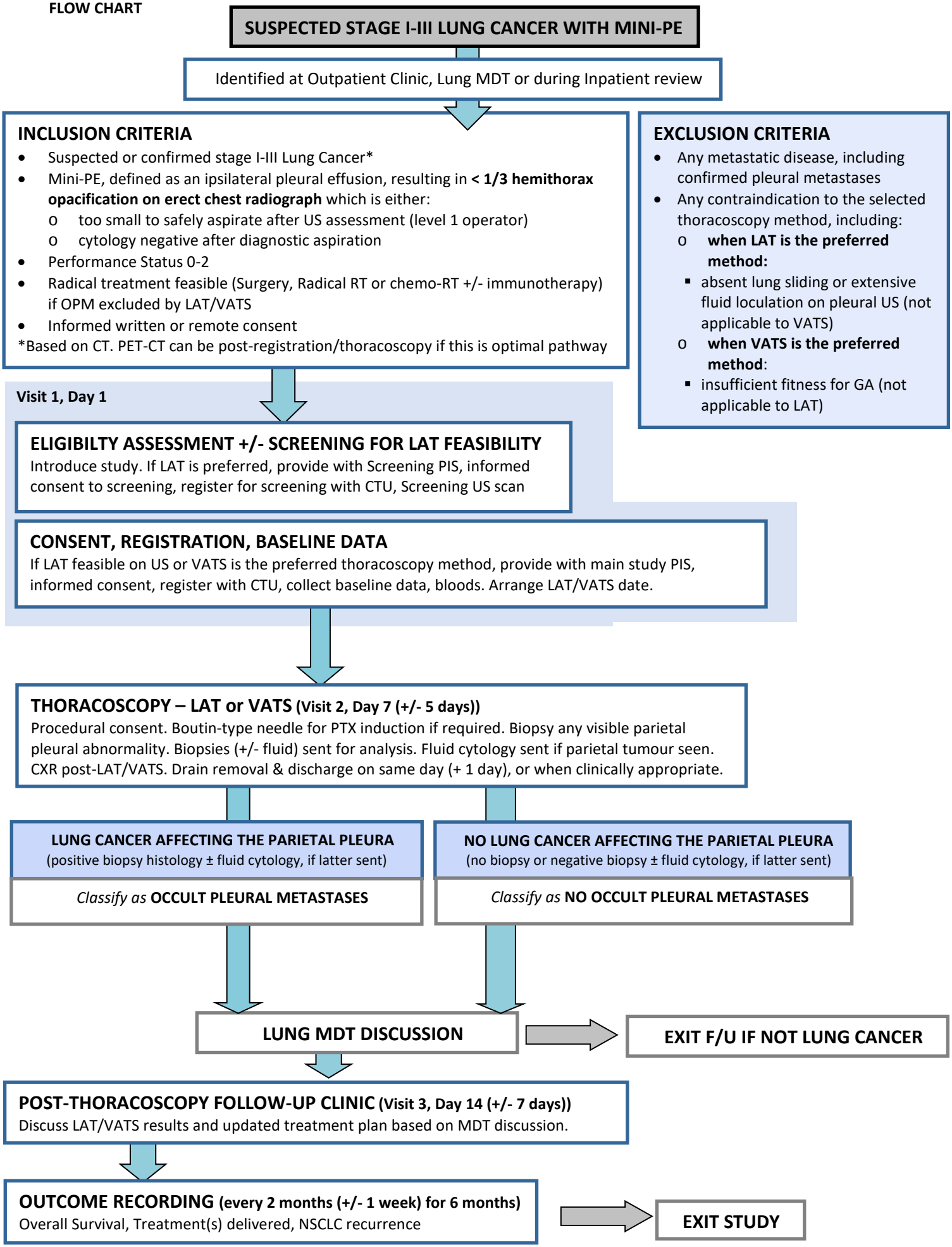
ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
CaCTUS	Cancer Clinical Trials Unit Scotland
CI	Chief Investigator
CRF	Case Report Form
CRUK	Cancer Research United Kingdom
CT	Computed Tomography
CTC	Clinical Trial Coordinator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
GA	General Anaesthetic
GP	General Practitioner
HRA	Health Research Authority
IB	Investigator Brochure
IDMC	Independent Data Monitoring Committee
LAT	Local Anaesthetic Thoracoscopy
MDT	Multi-Disciplinary Team Meeting
Mini-PE	Minimal Pleural Effusion
NSCLC	Non-Small Cell Lung Cancer
OPM	Occult Pleural Metastases
OS	Overall Survival
PET-CT	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PIS	Patient Information Sheet
PLC	Pleural Lavage Cytology
PM	Project Manager
PNF	Pregnancy Notification Form
PS	Performance Status
PV	Pharmacovigilance
RFS	Recurrence Free Survival
R&D	Research and Development
RAE	Related Adverse Event

Abbreviation	Term
REC	Research Ethics Committee
RSI	Reference Safety Information
RT	Radiotherapy
SAE	Serious Adverse Event
SRAE	Serious and Related Adverse Event
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSC	Trial Steering Committee
US	Ultrasound
VATS	Video-assisted Thoracoscopic Surgery

FLOW CHART


SUSPECTED STAGE I-III LUNG CANCER WITH MINI-PE
Identified at Outpatient Clinic, Lung MDT or during Inpatient review
INCLUSION CRITERIA
Suspected or confirmed stage I-III Lung Cancer*
Mini-PE, defined as an ipsilateral pleural effusion, resulting in < 1/3 hemithorax opacification on erect chest radiograph which is either:
too small to safely aspirate after US assessment (level 1 operator)
cytology negative after diagnostic aspiration
Performance Status 0-2
Radical treatment feasible (Surgery, Radical RT or chemo-RT +/- immunotherapy) if OPM excluded by LAT/VATS
Informed written or remote consent
*Based on CT. PET-CT can be post-registration/thoracoscopy if this is optimal pathway
EXCLUSION CRITERIA
Any metastatic disease, including confirmed pleural metastases
Any contraindication to the selected thoracoscopy method, including:
when LAT is the preferred method:
absent lung sliding or extensive fluid loculation on pleural US (not applicable to VATS)
when VATS is the preferred method:
insufficient fitness for GA (not applicable to LAT)
Visit 1, Day 1
ELIGIBILTY ASSESSMENT +/- SCREENING FOR LAT FEASIBILITY
Introduce study. If LAT is preferred, provide with Screening PIS, informed consent to screening, register for screening with CTU, Screening US scan
CONSENT, REGISTRATION, BASELINE DATA
If LAT feasible on US or VATS is the preferred thoracoscopy method, provide with main study PIS, informed consent, register with CTU, collect baseline data, bloods. Arrange LAT/VATS date.
THORACOSCOPY – LAT or VATS (Visit 2, Day 7 (+/- 5 days))
Procedural consent. Boutin-type needle for PTX induction if required. Biopsy any visible parietal pleural abnormality. Biopsies (+/- fluid) sent for analysis. Fluid cytology sent if parietal tumour seen. CXR post-LAT/VATS. Drain removal & discharge on same day (+ 1 day), or when clinically appropriate.
LUNG CANCER AFFECTING THE PARIETAL PLEURA
(positive biopsy histology ± fluid cytology, if latter sent)
Classify as OCCULT PLEURAL METASTASES
NO LUNG CANCER AFFECTING THE PARIETAL PLEURA
(no biopsy or negative biopsy ± fluid cytology, if latter sent)
Classify as NO OCCULT PLEURAL METASTASES
LUNG MDT DISCUSSION
EXIT F/U IF NOT LUNG CANCER
POST-THORACOSCOPY FOLLOW-UP CLINIC (Visit 3, Day 14 (+/- 7 days))
Discuss LAT/VATS results and updated treatment plan based on MDT discussion.
OUTCOME RECORDING (every 2 months (+/- 1 week) for 6 months)
Overall Survival, Treatment(s) delivered, NSCLC recurrence
EXIT STUDY

SCHEDULE OF ASSESSMENTS

Visit Number	V1 Baseline	V2 LAT/VATS	V3	Remote F/U
Approximate Study Day	1[a]	7 (±5)	14 (±7)	2 mthly (+/- 1 wk) for 6 mths
Study Activity				
Review Eligibility Criteria	X			
Introduce study if potentially eligible [a]	X			
If LAT is preferred method, provide with Screening Patient Information Sheet [b]	X [b]	X [c]		
Informed written or remote consent to LAT Screening [d]	X [a]	X [c]		
Register patient for LAT Screening with CTU [b]	X [a]	X [c]		
LAT Screening Pleural Ultrasound scan [b, e]	X [a]	X [c]		
If eligible after LAT screening or if VATS preferred thoracoscopy method, provide with main study Patient Information Sheet	X	X [c]		
Discussion regarding participation (offer call ≤ 48h if more time required) [f]	X			
Arrange date for LAT or VATS [g]	X			
Informed written or remote consent for main study [d]	X	X [c]		
Register patient for main study with CTU	X	X [c]		
Baseline Chest Radiograph	X	X [c]		
Blood Sampling, Processing and Banking [h]	X	X [c]		
Record Baseline Data, including Stage & Treatment plan	X	X [c]		
Admission for Thoracoscopy (LAT or VATS)		X		
Thoracoscopy (LAT or VATS) including biopsy of any parietal pleural abnormality [j]		X		
Pleural fluid samples sent for cytology if visible parietal tumour; if not, fluid processed and banked but cytology not sent [h, i]		X		
Chest radiograph following thoracoscopy (within 1-12 hours)		X		
Discharge home (ideally same day or ≤24h of thoracoscopy)		X		
Lung MDT discussion; review LAT/VATS results and document oncological treatment plan			X	
Clinic visit to discuss outcome of LAT/VATS and treatment plan			X [j]	
Chest radiograph			X	
Record post-LAT/VATS staging and treatment plan			X	
Record Adverse Events	X	X	X	
Record Adverse Events, Survival, Treatment(s) +/- Recurrence				X [k]

a. Investigators may introduce the study at earlier visits if eligibility likely and clinically appropriate. Can be done virtually depending on local arrangements
b. Screening is only necessary if LAT is the preferred thoracoscopy method. Therefore, all screening activities, including provision of screening PIS and attendance for screening US scan can be omitted if VATS is preferred.
c. If not performed at Visit 1
d. Consent can be written or remote (via telephone or video-call). If consenting remotely, the PIS must have been provided by post/email and the study must have been explained to the patient. The patient must have had the opportunity to ask any questions regarding the study. This must be fully documented in the patient notes.
e. Please refer to STRATIFY Ultrasound Manual
f. Patients will be offered a follow-up telephone call with a member of the study team, within 48h of Visit 1, if they need more time to consider the study.. LAT/VATS date will be arranged if the patient wishes to proceed
g. COVID swab may be required pre-LAT/VATS admission, depend on current local policies
h. Please refer to STRATIFY Sample Handling Manual
i. Please refer to STRATIFY Thoracoscopy Manual
j. Can be via video/ telephone call depending on local arrangements –MDT does not need to be on same day as clinic
k. Patient attendance is not required for 2-monthly follow up visits

INTRODUCTION

1.1 Background

Lung Cancer is the commonest cause of cancer-related death in Scotland, accounting for more than 1 in 5 cases. In 2012 there were 35,000 deaths from Lung Cancer across the UK. Despite major advances in staging and potentially curative (or radical) treatments (surgery and radiotherapy (RT)), recurrence rates remain unacceptably high. In patients with Stage I, II and IIIA Non-Small Cell Lung Cancer (NSCLC) 2-year mortality is currently 15%, 30% [1] and 50%[2], 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[3,4]. 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[3,5,6], 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[7,8]. We will prospectively evaluate LAT as a pleural staging tool in NSCLC and explore alternative mechanisms for poor outcomes.

Minimal Pleural Effusion (Mini-PE) has been defined as a small pleural collection ipsilateral to the primary tumour, which is either too small to safely aspirate for a cytology sample, or one that has been aspirated and the initial fluid cytology is negative (see Figure 1, below, for examples). Mini-PE affects up to 25% of patients presenting with NSCLC[4], although half of these occur in patients with metastatic disease[3,4].

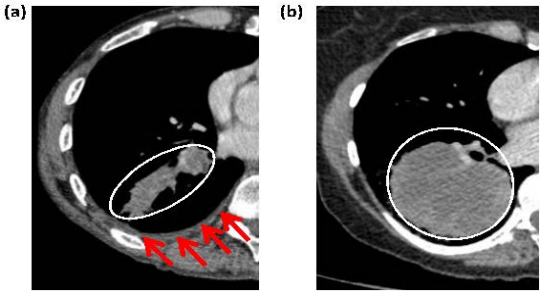


Figure 1. CT images from patients with: (a) T2b N1 M0 (Stage 2A) NSCLC and Mini-PE (red arrows). Median OS 35%, HR for death 2.24 relative to T2b N1 without Mini-PE[4] (b) T3 N1 M0 (Stage 2B) NSCLC without Mini-PE. Median OS 55%[4]-64%[1]. Both patients have potentially radically treatable disease (circled).

Since 2014, two large retrospective series have described clear association between excess mortality following radical treatment for Stage I-IIIA NSCLC and Mini-PE on diagnostic (pre-treatment) CT imaging, see Figure 2. These series conclude that Mini-PE reflects occult pleural metastases in up to 80% of patients[3,4]. However, this is based on indirect evidence and supportive follow-up imaging. In both series, it is acknowledged that other

factors may have contributed to the adverse survival observed, including benign pleuritis, systemic co-morbidities[9,10] and under-treatment due to nihilism due to the suspicion of OPM[3,4].

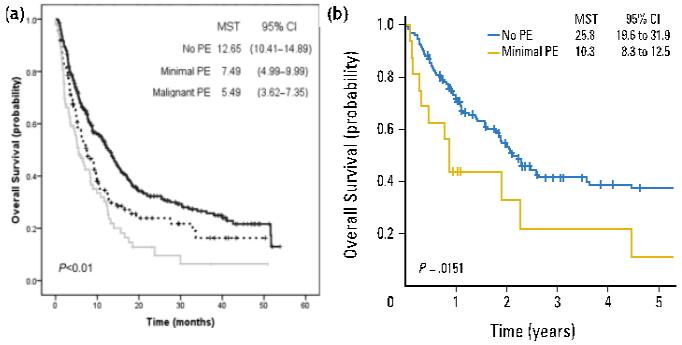


Figure 2. Kaplan-Meier Survival curves reported by: (a) Porcel[4] (n=490; 225 with Mini-PE) (b) Ryu[3] (n=2061; 272 with Mini-PE). The prognostic impact of Mini-PE was inversely related to Stage (Hazard Ratio for death was 2.1, 2.2, 1.6 in Stages I, II and III, respectively). Stage II cases are shown in Figure 2 (b) for illustration.

In late 2015, an audit was performed of 302 consecutive patients, who presented with NSCLC to Glasgow centres between January and June 2008. The audit reviewed staging and all diagnostic imaging acquired prior to treatment and dichotomised patients with radically treatable NSCLC (Stages I-IIIA, 127/302) into groups with Mini-PE (20/127) and no pleural effusion (107/127). Stage, Performance Status (PS), co-morbidities (summarised by the Charslon Comorbidity Index (CCI), NSCLC treatment(s) delivered and Overall Survival were also recorded. A survival analysis was performed (see Figure 3), and the presence of Mini-PE against PS, CCI and NSCLC treatments delivered was correlated.

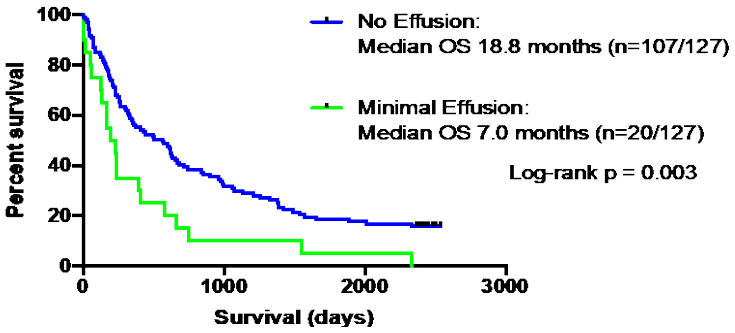


Figure 3. Kaplan Meier survival analysis of 127 consecutive patients who presented to Glasgow clinics with radically treatable NSCLC (Stage I-IIIA) between January and June 2008.

A marked survival disadvantage was found in patients with Mini-PE, as previously shown[3,4]. These were also characterized by trends to association with worse PS (1.9 vs. 1.4, p=0.07) and higher CCI (1.1. vs. 0.4, p= 0.07) in agreement with Ryu[3]. More conservative treatment was found (more supportive care/palliative RT, less surgery, no radical RT, less chemotherapy) in patients with Mini-PE, although the small numbers precluded meaningful statistical analyses. From these data, Mini-PE appears to confer excess mortality risk. It also appears likely that most patients have OPM, but some do not. The latter is supported by the notable tail on the Mini-PE survival curves in Figures 2 and 3, suggesting that 10-20% of patients survive for 2-3 years. The data also suggest that patients without OPM may be receiving over-cautious therapy because of inaccurate staging. Precise pleural staging would therefore protect patients with OPM from toxicities associated with radical treatments that cannot cure them and encourage radical treatment in patients who can benefit.

1.2 Trial Rationale

1.2.1 Current Approach to Pleural Staging of Lung Cancer

The current NICE guidelines (CG 121, 2011) do not specifically address pleural staging, while the current ACCP guidelines (2013) and SIGN guidelines (SIGN 137, 2014) suggest 'a pleural biopsy should be considered' in patients with an effusion consistent with Mini-PE, without specifying a modality or biopsy technique. Lung Cancer teams are therefore reliant on CT, PET-CT and Pleural Aspiration cytology (if this can be performed), all of which are negative by definition in patients with Mini-PE. Even in patients with larger, symptomatic pleural effusion, CT is limited by a sensitivity of 68% (95% CI 62% to 75%), with a low negative predictive value (65% (58% to 72%))[11,12]. With regard to semi-quantitative PET-CT, a recent meta-analysis concluded this should not be used for pleural staging, based on a pooled sensitivity of 81% (specificity of 74%)[13], and recommended further studies, particularly in Mini-PE. All STRATIFY participants will have contrast-enhanced CT prior to registration and thoracoscopy. However, PET-CT can be completed after registration and after thoracoscopy, if this is the optimal pathway in the judgement of the site PI. There are no previously published data regarding the potential for false positive PET-CT pleural findings following thoracoscopy for Mini-PE (excluding previous reports related to pleurodesis, which are not relevant here). Nevertheless, this is considered sufficiently unlikely to allow the optimal sequencing of these tests to be decided on a per participant basis.

1.2.2 Local Anaesthetic Thoracoscopy

VATS thoracoscopy involves general anaesthesia and is a potentially highly sensitive staging tool[6] In previous studies, VATS has been combined with pleural lavage cytology (PLC, which involves saline irrigation during surgery in patients without an effusion)[14]. However, VATS is not a practical option for all patients, in whom non-surgical treatments are frequently required due to comorbidities or patient choice. In addition, the significance of PLC results is not clear, since positive results might not necessarily preclude surgical resection[15]. Using current methods, pleural staging is therefore an overly subjective process, with treatment decisions based on incomplete data. Instinctively, clinicians have tended to give patients 'the benefit of the doubt', preferring to risk missed metastatic disease than deny a patient 'potentially' radical treatment. However, the adverse prognosis recently associated with Mini-PE demands a more objective strategy, particularly considering the toxicities of radical treatment. Additional data is particularly needed regarding the use and safety of LAT in this mini-PE since it is plausible that most patients could be staged by this technique, without recourse for VATS. Local Anaesthetic Thoracoscopy (LAT) is the gold-standard diagnostic test for patients with larger, symptomatic effusions and offers diagnostic sensitivity of 93% (95% CI 91% to 94%) and a major complication rate of only 2.3% (95% CI 1.9% to 2.8%)[7]. LAT can be performed as a day-case in patients with minimal/no pleural effusion but its performance and safety profile may differ when deployed in mini-PE and this role has never been prospectively evaluated. STRATIFY will determine the true prevalence of OPM using either LAT or VATS, with sites encouraged to offer LAT when it is technically feasible. This will be assessed at a dedicated screening visit when LAT is the method preferred by the local team.

2 TRIAL OBJECTIVES

2.1 Primary Objective

To determine the true prevalence of detectable OPM in patients with suspected or confirmed Stage I-III lung cancer and Mini-PE

2.2 Secondary Objectives

- To determine the impact of thoracoscopy results on Recurrence Free Survival (RFS) and Overall Survival (OS) in patients with Stage I-III lung cancer and Mini-PE
- To determine whether thoracoscopy is feasible and safe in patients with stage I-III lung cancer and Mini-PE
- To determine the impact of thoracoscopy results on treatment plans in patients with stage I-III lung cancer and Mini-PE

2.3 Exploratory Objective

- To determine the diagnostic performance of blood/pleural fluid biomarkers for OPM and/or adverse outcomes in subsequent studies

3 TRIAL DESIGN

This multi-centre observational trial will be performed according to the UK Policy Framework for Health and Social Care Research

3.1 Trial Population

3.1.1 Cases of Mini-PE

STRATIFY will prospectively recruit 50 patients with suspected or confirmed stage I-III lung cancer and Mini-PE. The definition of Mini-PE is specified in the eligibility criteria. We estimate that ≤15% will have detectable OPM, based on an interim analysis of the first 12 STRATIFY recruits. This represents a change in estimated prevalence, which was initially set at 70%, reflecting solely the retrospective data previously reported[3,4].

3.2 Eligibility Criteria

All patients will be subject to the following eligibility criteria. There will be no exception to the eligibility requirements at the time of registration. Queries in relation to the eligibility criteria should be addressed via contact with the CTU prior to registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria apply.

3.2.1 Inclusion Criteria

- Suspected or confirmed stage I-III lung cancer*
- Mini-PE, defined as an ipsilateral pleural effusion, resulting in **< 1/3 hemithorax opacification on erect chest radiograph** which is either:
  a) too small to safely aspirate after US assessment (level 1 operator judgement)
  b) cytology-negative after diagnostic aspiration
- Performance Status 0-2
- Radical treatment feasible (Surgery, Radical RT or chemo-RT +/- immunotherapy) if OPM excluded by thoracoscopy (local PI judgement)
- ≥ 16 years of age
- Informed written or remote consent

** All participants will have contrast-enhanced CT prior to registration. PET-CT can be completed after registration and after thoracoscopy if this delivers the optimal pathway for the patient. In most centres, it is expected that PET-CT will also occur pre-registration and pre-thoracoscopy.*

3.2.2 Exclusion Criteria

- Any metastatic disease, including confirmed pleural metastases**
- Any contraindication to the selected thoracoscopy method, including:
  - when LAT is the preferred method:
    - absent lung sliding or extensive fluid loculation on pleural ultrasound (not applicable to VATS)
  - when VATS is the preferred method:
    - insufficient fitness for general anaesthesia (not applicable to LAT)
- Uncorrectable bleeding disorder (applicable to LAT and VATS)

** Patients with **bilateral pleural effusions are not excluded** but there should be sufficient suspicion of OPM to justify thoracoscopy (in the opinion of the PI), e.g., a larger effusion ipsilateral to the primary disease

3.3 Identification of participants and consent

3.3.1 Cases of Mini-PE

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 sought, via telephone or videoconference. The study must have been adequately explained to the patient and the patient must have had had the opportunity to ask questions. This must be fully documented in the patient notes. When the subject attends for 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.

3.4 Registration

Patients cannot be screened or registered until the site has been activated to begin recruitment.

3.4.1 Screening Entry

As patients are identified for the trial and once informed consent has been given, patients undergoing LAT require to be entered for screening. To enter a patient for screening on the trial, please contact the CRUK Clinical Trials Unit, Glasgow by either telephone or email:

Telephone Number: 0141 301 7952

Email: ggc.recruitment.crukglasgowctu@nhs.scot

Opening Hours: 08.30-17.00 Monday -Thursday, Friday 08.30-16.30, except public holidays

A screening number will be allocated at this point.

3.4.2 Registration – Main study

Once screening (if required) has been completed, eligible patients who wish to participate should be registered. To register a patient, contact the CRUK Clinical Trials Unit, Glasgow by either telephone or email:

Telephone Number: 0141 301 7952

Email: ggc.recruitment.crukglasgowctu@nhs.scot

Opening Hours: 08.30-17.00 Monday-Thursday, Friday 08.30-16.30, except public holidays

The patient's eligibility criteria will be checked and, if eligible, a trial number will be allocated at this point.

All patients must be screened (if required) and registered onto the trial prior to commencement of trial activity.

With the patient's consent, their GP will be informed of their involvement in the trial.

3.5 Withdrawal of Patients from the Trial

Patients have the right to withdraw from the trial at any point for any reason. Similarly, the investigator may withdraw patients from the trial in the event of an intercurrent illness, the patient no longer being fit for trial procedures (including LAT/VATS), AEs, SAEs, SUSARs, protocol violations or any other relevant reason. If a patient withdraws from the trial itself, it should be clearly documented in the patient's notes what they are withdrawing from (consent to use any past data, consent to use any samples collected or consent for further data collection from the date of consent withdrawal). If a patient withdraws their consent from the trial, the site must contact the CTU with full details of the withdrawal. Where applicable, the CTU may ask the site to complete a Consent Withdrawal Form to record full details of the consent withdrawal.

3.6 Co-enrolment Guidelines

If sites wish to recruit patients to any interventional studies, the Sponsor and Trial Management Group will consider this on a study-by-study basis and where required request ethical approval to allow co-enrolment. It is imperative that the Sponsor of the other study is also contacted and approves co-enrolment within their study.

4 TRIAL PROCEDURES

4.1 Trial Endpoints

4.1.1 Primary Endpoint

The primary endpoint is the prevalence of detectable OPM, defined as the proportion of patients with lung cancer affecting the parietal pleura, based on LAT or VATS sampling. This sampling will include parietal pleural biopsies, supplemented by pleural fluid cytology when macroscopic parietal pleural tumour is visualised.

4.1.2 Secondary Endpoints

The following secondary endpoints will address the secondary research objectives:

Secondary Objective	Associated Endpoints
To determine the impact of thoracoscopy results on Recurrence Free Survival (RFS) and Overall Survival (OS) in patients with stage I-III lung cancer and Mini-PE	• Thoracoscopy results, recorded as: OPM demonstrated/not demonstrated • RFS, defined as the time from completion of lung cancer treatment to recurrence or death from any cause • OS, defined as the time from thoracoscopy to death from any cause
To determine whether LAT is feasible and safe in patients with stage I-III lung cancer and Mini-PE	• LAT feasibility, recorded as: complete/incomplete/not feasible/ • VATS feasibility, recorded as: complete/incomplete/not performed • Safety, as assessed by Adverse Event (AE) and Serious AE (SAE) rates

To determine the impact of thoracoscopy results on treatment plans in patients with stage I-III lung cancer and Mini-PE	• Thoracoscopy results, recorded as: OPM demonstrated/not demonstrated • The treatment plan pre-registration • The treatment plan at Lung MDT following thoracoscopy

4.1.3 Exploratory Endpoints

The following exploratory endpoint will address the exploratory research objective:

Exploratory Objective	Exploratory Endpoint
To determine the diagnostic performance of blood/pleural fluid biomarkers for OPM and/or adverse outcomes in subsequent studies	Venous blood and pleural fluid samples will be collected but not analysed in this study

4.2 Trial Schedule

4.2.1 Screening/Baseline: (Visit 1, Day 1)

Main Study Activity

- Review Eligibility Criteria, and introduce study if potentially eligible (Investigators may introduce the study at earlier clinic visits, including virtual clinics, if eligibility likely and clinically appropriate)
- If LAT is the preferred thoracoscopy method*:
    - Provide with Screening Patient Information Sheet
    - Informed written or remote consent to Screening
    - Register patient for Screening with CTU and obtain Screening number
    - Screening Pleural Ultrasound scan (see STRATIFY Ultrasound Manual)
- If eligible after LAT screening or if VATS is the preferred thoracoscopy method, provide with main Study Patient Information Sheet
- Informed written or remote consent to main Study**
- Register patient with CTU**
- Baseline chest radiograph**
- Blood Sampling, Processing and Banking** (see STRATIFY Sample Handling Manual)
- Record Baseline Data, including Stage and Treatment plan**
- Record any screening adverse events**

** Screening activities are only necessary if LAT is the preferred thoracoscopy method. All screening activities, including provision of screening PIS and attendance for screening US scan can be omitted if VATS is planned*

*** Patients may choose to defer consent if they required additional time to consider involvement. Patients will therefore 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. Consent to the main study, registration, baseline chest radiograph, blood sampling and recording of baseline data can then occur at Visit 2. Remote consent must be fully documented in the patient case notes, and written consent collected at the first face to face clinic visit.*

4.2.2 Visit 2 Thoracoscopy by LAT or VATS: (Day 7 (±5 days))

In addition to the Visit 2-specific activities outlined below, Visit 2 affords another opportunity for uncompleted Visit 1 activities. This can include, when LAT is the preferred thoracoscopic method provision of screening PIS, consent and registration for screening pleural ultrasound plus provision of main study PIS, consent and registrations (see section 4.2.1 for details). This option may be particularly suitable for patients initially seen virtually for their first clinic appointments and for patients who require additional time to consider their involvement.

- Admission for thoracoscopy (LAT or VATS)
- Informed written consent to main Study (if not already performed at Visit 1 or 2, or if consent given remotely)
- Register patient with CTU (if not already performed at Visit 1 or 2)
- Baseline chest radiograph (if not already performed at Visit 1 or 2)
- Blood Sampling, Processing and Banking (if not performed at Visit 1 or 2)
- Record Baseline Data, including Stage and Treatment plan (if not performed at Visit 1 or 2)
- LAT/VATS, including biopsy of any parietal pleural abnormality (see STRATIFY Thoracoscopy Manual)
- Pleural fluid samples sent for cytology if visible parietal tumour; if not, fluid to be processed and banked (see STRATIFY Thoracoscopy Manual, and STRATIFY Sample Handling Manual)
- Chest Radiograph following LAT/VATS (within 1-12 hours)
- Discharge Home (may occur up to 1-day post-LAT/VATS or when clinically appropriate)
- Record any adverse events

4.2.3 Visit 3 Post-Thoracoscopy: (Day 14 (±7 days))

- Lung MDT discussion: review LAT/VATS results and confirm treatment plan
- Clinic visit to discuss outcome of Lung MDT discussion (does not need to be on the same day as the MDT; can be done as face to face or virtual consultation depending on local arrangements)
- Chest Radiograph
- Record post-LAT/VATS staging, treatment plan and any adverse events

4.2.4 Remote Follow Up Visits (2 monthly for 6 months +/- 1 week)

- Record any adverse events, overall survival, treatment(s) delivered and recurrence data
- No patient attendance is required for these visits

4.3 Laboratory Tests

Blood samples will ideally be drawn at Visit 1 but can be drawn at Visit 2, in patients who require more time to consider participation after initial discussion. Pleural fluid samples will be drawn at Visit 2. Immediate processing should be performed at each study centre (detailed instructions for sample collection and processing are provided in the STRATIFY Sample Handling Manual). Consumables supplied by the CRUK CTU are listed in the STRATIFY Sample Handling Manual. All samples will be labelled with a unique Trial Number and immediately stored in a -80 Freezer within 2 hours. Arrangements for the collection of samples from each centre will be coordinated by the CRUK Glasgow CTU.

4.4 Participation in concurrent clinical trials

Co-enrolment in another trial is not permitted until the primary endpoint has been reached at Visit 4. Beyond this, participation in other trials should be recorded on the 'Anti-cancer Treatment' eForm at follow up visits. If an exception is required to the above criteria the Principal Investigator seeking the exception should seek approval from the Chief Investigator (CI) and Trial Management Group prior to enrolling the patient in the other trial. It is imperative that the Sponsor(s) of both studies also approve co-enrolment within their trial.

5 ASSESSMENT OF SAFETY

5.1 Thoracoscopy Safety Profile

Local Anaesthetic Thoracoscopy (LAT) allows direct visualisation of abnormal areas of pleura, multiple biopsies to be taken and provision of definitive pleural effusion management, e.g., pleurodesis, in patients with symptomatic pleural effusion. In this clinical setting, LAT is well-tolerated and can be performed as a day-case. It offers high diagnostic sensitivity (sensitivity 92.6%, specificity 100% n=1369 cases) and is associated with a low complication rate (0% mortality in over 2000 diagnostic LAT cases across 28 studies and a 1.8% major complication rate in over 4500 LAT cases across 47 studies)[8]. The safety profile of LAT when used as a staging tool in patients with smaller pleural effusions is likely to be similar since many Level II Thoracoscopy centres routinely deliver LAT in patients with small (or no) pleural effusions equivalent to Mini-PE. This safety profile will be recorded prospectively in this study. Video assisted thoracoscopic surgery (VATS) offers similar high diagnostic sensitivity to LAT and is also safe with a low complication rate. However, the procedure requires general anaesthesia, intubation and single lung ventilation and is therefore not suitable for participants with

major comorbidities. In one large series (n=566), the most common side effect was subcutaneous emphysema with cardiac dysrhythmia and air embolism occurring in <1% and no deaths (Viksum et al, 1981).

6 SAFETY REPORTING

Only Adverse Events (AEs) and Serious Adverse Events (SAEs) thought related to trial procedures require recording and reporting. This includes AEs resulting from pleural ultrasound, chest radiographs, venous blood sampling and LAT/VATS. Safety reporting will be performed by the Pharmacovigilance Department of the CRUK CTU Glasgow as delegated by the trial Sponsor.

6.1 Definitions

As all study related screening procedures are routine and non-invasive the risk of AEs and SAEs occurring after consent to participate in the trial and before starting trial intervention, has been assessed as low. Therefore, these definitions apply to all trial participants from Visit 1 up to and including 180 days after the last intervention.

Term	Definition
Adverse Event (AE)	An adverse event (AE) is any untoward medical occurrence in a subject to whom a medicinal product is administered, which does not necessarily have a causal relationship with this treatment/intervention.
Related Adverse Event (RAE)	A related adverse event (RAE) is any untoward and unintended occurrence in a subject administered trial treatment/intervention which is thought to be caused by or related to the trial treatment/intervention.
Serious Adverse Event (SAE)	A serious adverse event (SAE) means any untoward medical occurrence that at any dose requires the following, whether or not considered related to the trial treatment. • Requires inpatient hospitalisation or prolongation of existing hospitalisation* • Results in persistent/significant disability or incapacity • Results in a congenital anomaly/birth defect • Is life-threatening (i.e. at the time of the event)** • Or results in death • Is considered medically significant by the Investigator*** * defined as a hospital admission required for treatment of an AE. No time frame is specified for the duration of the admission. ** the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death. *** events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Medical and scientific judgement should be exercised in deciding whether an event is "serious" in accordance with this criterion.

N.B: To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event (for example CTCAE grade), which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

6.2 Detecting, Recording and Reporting of Adverse Events

Sites must always record all AEs in the patient's notes even though they are not required to be recorded in the eCRF if the event is not considered to be related to a trial procedure (see Section 6.2.3). When investigators record AEs in the patient's notes, they should record the severity (CTCAE grade), seriousness and causality (relationship of the AE to the trial intervention).

6.2.1 Detection of Adverse Events

Participants will be asked at each trial visit about the occurrence of AEs since their last visit. AEs will be recorded, notified, assessed, reported, analysed and managed in accordance with the Health Research Authority (HRA) HTA requirements. AEs must be recorded as they are reported whether spontaneously volunteered or in response to questioning about well-being at trial visits. The questioning about AEs will cover the current visit as well as the period of time between the previous and the current visit. All AEs must be documented in full in the patient's medical records whether they are required to be recorded in the CRF or not.

6.2.2 Recording of Adverse Events

Full details of AEs including the nature of the event, start and stop dates, severity (CTCAE grade), seriousness and causality (relationship of the AE to the trial intervention) and outcome will be recorded in the patient's medical records and in/on the study case report form/MACRO system as required. AEs must be reported from Visit 1 and followed until:

- They resolve
- If present at pre-treatment, until the AE returns to the CTCAE grade observed at pre-treatment
- The AE is confirmed at unlikely to ever resolve

If none of the criteria above are met by 180 days following the last trial procedure, the AE no longer requires to be followed up. Perceived lack of efficacy is not an AE. An exacerbation of a pre-existing condition is an AE. The Investigator does not need to actively monitor patients for AEs once the trial has ended, unless required.

6.2.3 Assessment of Adverse Events

All AEs and must be coded and graded according to the NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) Version 5.0. These criteria can be accessed via the National Cancer Institute Website. AEs must be assessed for seriousness, causality and severity. This assessment is the responsibility of the Investigator (or medically qualified designee). In determining whether an AE is related to a trial procedure, an adverse reaction, Investigators must consider if there is a reasonable possibility of establishing a causal relationship between the event and the trial intervention (i.e., LAT, VATS, based on their analysis of all the available evidence). The assessment must be based on anticipated effects of these interventions, as specified in the protocol, or related to the patient's disease, either the disease under investigation or a concurrent illness. The investigator must, whenever possible, provide a causality assessment for AEs based on the information available at reporting and their knowledge of the disease and the effects of the study procedure(s). The Chief Investigator (CI) shall not downgrade the causality assessment provided by an Investigator. Although Investigators must record all AEs in the patient notes they are only required to record AEs on the eCRF for events that are a result of a protocol related procedure.

6.2.4 Reporting of a Serious Adverse Event

Investigators are only required to report Serious Adverse Events (SAEs) if they are the result of a protocol procedure as outlined in section 6, meet the regulatory definition of serious (see Section 6.1) and are not listed as expected (see list of expected events below in Section 6.2.5). Investigators must report all SAEs to the Pharmacovigilance Office, CRUK CTU immediately and under no circumstances should this exceed 24 hours following first awareness of the event by the Investigator or site staff.

Email: mvls-ctu-pv@glasgow.ac.uk

Telephone: 0141 211 3567/0203/3969 or 232 2068

The purpose of this obligation is to ensure the CI on behalf of the Sponsor, has the necessary information to continuously assess the benefit-risk balance of the clinical trial. For guidance on submitting and completing the initial and follow up SAE forms please refer to the SAE Completion Guidelines, which will be provided by the Pharmacovigilance Office, CRUK CTU, Glasgow. The CI will receive notification, by email, of all SAEs received. SAEs must be reported locally by the PI at each site in accordance with local practices at their site (i.e., R&D Office). A follow-up report must be submitted when the SAE resolves, is unlikely to change, or when additional information becomes available. If the SAE meets the criteria for expedited reporting to the REC, then follow up information must be provided as quickly as possible and in the timeframe requested by the CRUK CTU and CI. All follow-up information is required to be reported promptly and follow up reports must be submitted until all AEs listed on the initial SAE report resolve or will never resolve. A follow up report should also be submitted if additional AEs occur, or new information becomes available about previously reported AEs.

SAEs are required to be reported from Visit 1 for up to 180 days after the last trial procedure in that patient. Any event that meets the criteria of a SAE (including events that the Investigator thinks are medically important but maybe do not require hospitalisation or are fatal) that occur after this 180-day interval should also be reported, if the Investigator thinks these are a late consequence of the trial procedures. The Investigator must report such events as SAEs to the CRUK CTU Glasgow Pharmacovigilance Office without undue delay. Investigators must follow-up serious and related events, whether they are expected by providing follow-up SAE reports until the reaction has completely resolved or will never resolve. Note that further elective hospital admissions or emergency admissions or death due to disease progression or treatment toxicities do not require to be reported as part of the trial but must be recorded in the eCRF. For any questions relating to SAE reporting, please contact the Pharmacovigilance team:

Pharmacovigilance Office, CRUK CTU, Glasgow

Email: mvls-ctu-pv@glasgow.ac.uk

Telephone: 0141 211 3567/0203/3969 or 232 2068

Contact details are also provided at the front of the protocol and in the SAE completion guidelines.

6.2.5 Expected Events

The following list of events are expected as a result of the trial intervention.

6.2.5.1 Pleural ultrasound

Thoracic ultrasonography is non-invasive and not expected to present any additional risk to participants or result in any complications.

6.2.5.2 Chest Radiography

Chest radiography is non-invasive and not expected to present any additional risk to participants or result in any complications.

6.2.5.3 Venous Blood Sampling

Venous blood sampling is not expected to present any additional risk to participants or result in any complications.

6.2.5.4 Local Anaesthetic Thoracoscopy (LAT)

Common (1/10 to 1/100)

1. Pain
2. Post-procedural pneumonia
3. Subcutaneous emphysema
4. Minor haemorrhage (port site or biopsy site) not requiring any intervention or transfusion

Uncommon (1/100 to 1/1000)

1. Port site infection requiring antibiotics or pleural empyema
2. Hypotension during procedure requiring additional fluids and/or vasopressors
3. Atrial fibrillation
4. Haemorrhage (port site or biopsy site) requiring intervention during procedure and/or transfusion
5. Port site tumour growth during subsequent follow-up period
6. Post-procedural pneumothorax with an air leak that delays tube removal or prolongs admission
7. Failure of procedure

6.2.5.5 Video-assisted Thoracoscopic Surgery (VATS)

Common (1/10 to 1/100)

1. Pain
2. Post-procedural pneumonia
3. Subcutaneous emphysema
4. Minor haemorrhage (port site or biopsy site) not requiring any intervention or transfusion

Uncommon (1/100 to 1/1000)

1. Port site infection requiring antibiotics or pleural empyema
2. Hypotension during procedure requiring additional fluids and/or vasopressors

3. Cardiac arrhythmia, including atrial fibrillation
4. Air embolism
5. Haemorrhage (port site or biopsy site) requiring intervention during procedure and/or transfusion
6. Port site tumour growth during subsequent follow-up period
7. Post-procedural pneumothorax with an air leak that delays tube removal or prolongs admission
8. Failure of procedure
9. Complications of general anaesthesia, e.g., anaphylaxis or idiosyncratic reaction to anaesthetic drugs
10. Complications of intubation, including throat pain, mucosal ulceration, laryngeal injury, including hoarseness, tracheal injury

6.2.6 Identifying Events for Expedited Reporting

The assessment of SAEs for expedited reporting will be undertaken by the CTU and CI based on the list of expected events recorded in the trial protocol at the time the SAE report is received. When deciding if an event is unexpected consideration will be made by the CI as to whether the event adds significant information on the specificity, increase of occurrence or severity of a known, serious and related event that is already recognised and documented in the protocol.

6.2.7 Expedited Reports

CRUK CTU on behalf of the Sponsor is responsible for the expedited reporting of all serious, related and unexpected events to the REC, Sponsor and PIs and trial sites. The CI (or CI designee) is responsible for deciding if an event is unexpected and requires expedited reporting. The requirement for expedited reporting starts with the first REC approval of the trial within the EU. It ends with the completion of the trial for all patients recruited (from the EU). SAEs will be reported to the REC where in the opinion of the CI the event was **both**:

- Related – that is, it resulted from administration of any of the research procedures
- Unexpected– that is, the type of event is not listed in the protocol as an expected event

Reports of related and unexpected SAEs will be generated from the trial database and signed by the CI. The report will then be submitted within 15 days of the CRUK Clinical Trials Unit, Glasgow becoming aware of the event, using the 'Report of Serious Adverse Event form' for non-CTIMPs published by the Health Research Authority (HRA). If the assessment of causality provided by the investigator differs from that of the CI (assessment is made on behalf of the sponsor), the opinion of both the investigator and CI will be provided in the expedited report. Investigators will receive all expedited reports. The CI will assess if the risk-benefit assessment has been affected by each serious, related and unexpected event they identify. If the risk-benefit of participation is adversely affected, appropriate prompt action will be decided upon by the CI, Sponsor and Trial Steering Group and implemented by the Trial Management Group.

6.2.8 Annual progress report

An annual progress report including information on the safety of trial participants if relevant, will be prepared by the Project Manager and submitted to the REC.

6.2.9 Reporting to the Medicines and Healthcare Products Regulatory Agency (MHRA)

There is no statutory requirement to report SAEs to the MHRA for clinical research which does not fall under the requirements of the Medicines for Human Use (Clinical Trials) Regulations such as non-CTIMPs.

7 STATISTICS AND DATA ANALYSIS

7.1 Trial Design and Sample Size

STRATIFY is a multi-centre observational study. The target sample size of 50 patients will allow estimation of the prevalence of OPM, AE rate and the impact on treatment plans with 95% confidence interval bounds not exceeding 10% if the OPM prevalence is ≤15% .

Proportion (%)	CI lower	CI upper	CI width	Precision
0.05 (5%)	**-1.0%**	**11.0%**	**0.1208**	**6.0%**
0.10 (10%)	**1.7%**	**18.3%**	**0.1663**	**8.3%**
0.15 (15%)	**5.1%**	**24.9%**	**0.1979**	**9.9%**

This represents a change in estimated prevalence, which was initially set at 70% (requiring a minimum sample size of 96). The initial OPM estimate of 70% reflected solely the retrospective data previously reported. The updated OPM estimate and sample size calculation acknowledges data from the first 12 recruits to STRATIFY, of whom only one case of confirmed OPM has been observed (8.3% OPM rate). Importantly, reduction in the sample size from 96 to 50 cases means the trial will no longer have adequate power (80%) to detect an overall survival (OS) hazard ratio of 0.5 as planned in previous iterations of this protocol. This original HR corresponded to data from previous retrospective studies, which reported a median OS in OPM +ve 6.32 months v 12.65 months in OPM –ve cases. OS differences between OPM +ve and OPM -ve groups will be assessed. Post hoc power calculations taking account of the observed prevalence will be performed.

7.2 Analysis Plan

7.2.1 Primary Efficacy Analysis

The estimate of the proportion OPM +ve and the associated 95% confidence interval will use standard statistical methods. The confidence interval will be based on the Clopper-Pearson exact approach.

7.2.2 Secondary Efficacy Analysis

The estimate of the proportions of OPM demonstrated/ not demonstrated and LAT complete/ LAT incomplete and the associated 95% confidence intervals will use standard statistical methods. The confidence interval will be based on the Clopper-Pearson exact approach. The comparison of the RFS and OS between OPM +ve and OPM –ve patients will be illustrated with Kaplan-Meier curves; the hazard ratio will be estimated using Cox regression. Adverse event data and the oncological treatment plan will be summarised in tables and listings.

7.2.3 Exploratory Analyses

Numbers of recruits with banked samples suitable for later analysis will be reported but no other analysis will be performed under this protocol.

7.2.3 Safety Analysis

Adverse event data will be summarised in tables and listings.

7.2.4 Interim Analysis

There are no planned interim analyses; the data will be analysed once at the end of the study.

8 TRIAL CLOSURE/DEFINITION OF END OF A TRIAL

The end of trial definition will be the date of last data capture. Date of last data capture will be met when all outstanding data has been returned from all sites, all required data queries have been resolved and the database is finalised to allow analysis to take place to answer all protocol endpoints.

8.1 End of Trial Notification/Declaration of the End of a Study Form

An end of trial notification will be submitted to the ethics committee within 90 days using the 'Declaration of the end of a study' form However if the trial is terminated either (1) before the date for the conclusion of the trial specified in the protocol for that trial or (2) before the number of events required by the trial has occurred, the ethics committee will be notified in writing of the termination of the trial within 15 days of the date of termination with a clear explanation of reasons and details of follow-up measures, if any, taken for safety reasons.

8.2 Clinical Trial Summary Report

The CI in association with CRUK CTU is responsible for compiling and submitting the final report to both sponsor and the REC.

8.3 Temporary Halt of the Trial

If recruitment to the trial needs to be temporarily halted for reasons not specified in the protocol the Sponsor will inform the REC immediately and at the latest within 15 days from when the trial is temporarily halted. This

includes trials where the stoppage was not envisaged in the approved protocol and where there is an intention to resume it. It does not include trials where recruitment may be temporarily halted for logistical reasons such as trial team availability. The notification will be made as a substantial amendment and will clearly state what activities have been halted and the reasons for this. To restart a trial that has been temporarily halted the Sponsor will make a request as a substantial amendment providing evidence that it is safe to restart the trial. If the Sponsor decides not to recommence the trial the REC will be notified in writing within 15 days of the decision, using the end-of-trial declaration form.

8.4 Early Termination of a Trial

In the case of early termination, the Sponsor will notify the end of a trial to the REC immediately and at the latest within 15 days after the trial is halted, explaining the reasons and describing the follow-up measures, if any, to be taken for safety reasons. This does not include trials that complete early because full recruitment has been achieved.

9 DATA HANDLING

9.1 CRFs

The CRFs for this trial will be completed using the electronic remote data capture (eRDC) system, MACRO®. Prior to recruitment beginning at each site, the MACRO® User Guide will be sent to sites. It is the responsibility of the Principal Investigator to ensure eCRFs are completed in a timely manner (within 4-6 weeks of the study visit) and to review and approve all data captured on the eCRF. **Please ensure that all data submitted on eCRFs are verifiable in the source documentation or that any discrepancies are recorded and explained.**

In addition to completing the MACRO® database there will be some paper CRFs, the screening and registration forms should be completed on the paper form prior to faxing or calling CRUK CTU. The SAE form will also continue to be on paper. Please review to the data completion guideline document in the ISF. Please also note that some study forms must be signed by the PI or another clinician delegated to do so on the delegation log. These forms will be defined in the completion guidelines.

Other essential documents, including source data, consent forms, and regulatory documentation, will be archived by, or for the Investigator, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

9.2 Central Review of Data

CRUK CTU will regularly review the data for compliance with the protocol, and for inconsistent or missing data. Should any missing data or data anomalies be found within the eCRFs upon CTU review, queries will be generated within the MACRO® study database for the site to access and resolve. Sites are expected to review and respond to queries within the database in a timely manner (within 4-6 weeks). Any issues identified at sites in relation to poor data/slow response to data queries will be managed as per the data escalation process below.

9.3 Data Escalation Processes

Where issues with data return/quality/response to requests are identified at sites, the following process will be followed:

- Step 1: E-mail letter to site main contact and copy in site PI
- Step 2: E-mail letter direct to site PI and copy in site main contact
- Step 3 E-mail letter to Network Coordinator and copy in site PI and main contact
- Step 4: Discuss suspension of recruitment at site until data issues resolved

9.4 Record Retention and archiving

Archiving of the trial essential documents should be performed by both the participating trial site and Sponsor/CRUK CTU.

Participating sites are responsible for archiving their trial related documentation and should follow the requirements of their R&D Office in conjunction with advice from the CRUK CTU and Sponsor regarding the duration of document retention. Sites should not archive their trial documentation until they have been instructed by the CRUK CTU or Sponsor that they are able to do so. Where possible, at the time of archiving, sites will be notified of the archiving retention period. If this is not confirmed at the time of archiving, sites should not destroy archived documentation until authorisation is given from the Sponsor.

The Sponsor and CRUK CTU will be responsible for archiving the Trial Master File (TMF) and all other essential trial documentation that is not held at participating trial sites as per their applicable SOPs.

If a patient's care is transferred to another hospital a Patient Transfer Form must be completed by the original recruiting site (or the current site responsible for the patient) to request that the transfer is performed within the CTU and MACRO® system. The original recruiting site will be recognised with the recruitment of the patient. The original (or current) site will be responsible for ensuring all data is up to date prior to the transfer of the patient on the MACRO® system. Once the transfer has been processed, the new site will be responsible for

returning all outstanding trial documents from that point onwards including any outstanding data prior to the date of transfer.

10 TRIAL MANAGEMENT

10.1 Trial Start Up

Sites wishing to participate in the trial should contact CRUK CTU. A PI must lead the trial at each site and they will be responsible for providing CRUK CTU with all core documentation. Protocol training will be given to sites via initiation slides that will be provided to sites prior to the trial opening at that site. Once all the documentation is received at CRUK CTU Glasgow an initiation call will be performed and after this the site will be contacted by email or fax when they are activated and are able to recruit patients to the trial.

10.2 Core Documents

- Local R&D approval / Confirmation of capacity and capability
- Signed Clinical Trial Agreement
- Delegation and training log completed by all members of the study team and signed off by the PI
- CV and GCP certificates for the PI
- PIS, GP letter and patient results letter on local headed paper
- Completed site capability form
- Initiation acknowledgements from all members of the study team confirmation the protocol and initiation slides have been reviewed
- Normal ranges and accreditation certificates for biochemistry and haematology departments

10.3 Management of Protocol Deviations and Violations

10.3.1 Deviations

Organisations must notify the Sponsor (via CRUK CTU) of all deviations from the protocol or GCP immediately. The Sponsor requires a report on the incident(s) and a deviation form will be provided to site for completion. This should be completed by site as soon as possible and returned to the PM or CTM. If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the CRUK CTU trial team and Sponsor can be contacted immediately to discuss. The Sponsor will assess all incidents with respect to the criteria of a “serious breach”.

10.3.2 Serious Breach

Events that match the criteria of a “serious breach” will be reported to the REC within 7 days of the matter coming to the attention of the Sponsor. National Research Ethics Service SOP for Research Ethics Committees

(version 6.1, January 2015) defines a serious breach as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards of conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of trial subjects or the scientific value of the research. The report should include details of when the breach occurred, the location, who was involved, the outcome and any information given to the participants. The REC should also be informed of any further corrective or preventative action the Sponsor plan to take.

10.4 Trial Management Group (TMG)

The trial will be coordinated from CRUK CTU by the TMG. The TMG normally includes those individuals responsible for the day-to-day management of the trial. Members of the TMG include the CI, Co Investigators, Project Manager, Trial Statistician, Clinical Trial Monitor, Pharmacovigilance CTC, and Patient Representative. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

10.5 Umbrella Trial Steering Committee (UTSC)

The role of the UTSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. The UTSC should agree any significant protocol amendments, provide advice to the investigators on all aspects of the trial and have members who are independent of the investigators, in particular an independent chairperson. Decisions about continuation or termination of the trial or substantial amendments to the protocol are usually the responsibility of the UTSC.

11 REGULATORY ISSUES

11.1 Ethics Approval

The study will be conducted in line with the current Government, HRA and health board guidance regarding Covid-19. Favourable ethics approval will be sought for the trial from an authorised REC before any patients are entered onto this clinical trial. The CI will be responsible for updating the ethics committee of any new information related to the trial.

Each participating site will be responsible for obtaining their own local approval from their local R&D department prior to opening the study. For sites within England, HRA approval is also required. Participating sites will not be activated to recruitment until all documents have been returned and necessary approvals are in place. The CRUK CTU Glasgow will send a site opening email to site and activate the site on local system.
The trial will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

11.2 Consent

Consent to enter the trial must be sought from each participant only after full explanation has been given, an information sheet offered, and time allowed for consideration. Signed participant consent must be obtained, the consent forms should also be signed by the person carrying out the consent procedure at site, who must be detailed on the study specific delegation and training log as having authorisation. The PI is responsible for ensuring if the taking of consent is delegated to a designee, the designee is suitably qualified by training or experience to take informed consent.

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 sought, via telephone or videoconference. The study must have been adequately explained to the patient and the patient must have had had the opportunity to ask any questions they may have regarding the study. This must be fully documented in the patient notes. When the subject attends for 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.

The right of the participant to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the best interests of the participant, but the reasons for doing so must be recorded. In these cases, the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

An original completed consent form must be retained at each site in the appropriate section of the Investigator Site File, and a photocopy placed in the patient's medical records. All patients must be given either an original or a copy (as per local site practice) of the signed patient information sheet and consent form for their records. Consent forms must be retained on site and not submitted to the CRUK CTU.

In the event that new patient information sheets/consent forms are produced throughout the duration of the trial, it may be that patients already participating in the trial should be re-consented to the updated version of the patient information sheet. However, if the principal investigator decides that this is not in the best interests of the patient re-consent is not required. Decisions not to re-consent patients must be documented in the patient's medical records. Re -consent can be obtained face to face or remotely. For remote re-consent, the Patient Information Sheet can be posted or emailed to the patient and then remote re-consent sought, via telephone or videoconference. Updates to the study information must have been adequately explained to the

patient and the patient must have had had the opportunity to ask any questions they may have regarding the study updates. This must be fully documented in the patient notes.

11.3 Confidentiality

All information collected during the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the CRUK CTU. The CRUK CTU will comply with all aspects of the 1998 Data Protection Act and operationally this will include:

- Consent from participants to record personal details including initials, date of birth, GP name and address
- Appropriate storage, restricted access and disposal arrangements for patient's personal and clinical details
- Consent from participants for access to their medical records by responsible individuals from the research staff or from regulatory authorities, where it is relevant to trial participation
- Consent from participants for trial data to be used to evaluate safety and develop new research
- Where central monitoring of source documents by CRUK CTU (or copies of source documents) are required (e.g., scans or blood results), the patient's name must be obliterated by site before sending
- Where anonymisation of documentation is required, sites are responsible for ensuring only the instructed identifiers are present before sending to CRUK CTU
- If a participant withdraws consent from further trial treatment and / or further collection of data their samples will remain on file and will be included in the final trial analysis unless they specifically withdraw consent for this

11.4 Liability, Indemnity and Insurance

No special insurance is in place for patients in this trial other than standard NHS liability insurance providing indemnity against clinical negligence. This does not provide cover for non-negligence e.g. harm caused by an unexpected side effect of participating in a trial. The sponsors have responsibility for ensuring that financial cover for damages or compensation arising from no fault harm is available to patients, where applicable. The co-sponsor, University of Glasgow, maintains clinical trials insurance. Cover for this clinical trial has been agreed under the current policy. The Hospital Trust/Health Board at each participating site is responsible for:

1. Acts and omissions of its own staff and others engaged by it, including the Clinical Trials Unit and PI;
2. Ensuring the appropriate insurance administered by the NHS Litigation Authority is in place
3. Ensuring any non-NHS employees involved in the clinical trial have Honorary Contracts with the Trust/Board to cover access to patients and liability arrangements.

These responsibilities are outlined and agreed within the Clinical Trial Agreement.

11.5 Sponsor

NHS Greater Glasgow and Clyde will act as the main sponsor for this trial. Delegated activities will be assigned to the CRUK CTU and NHS Trusts/Boards taking part in this trial. Details of responsibilities will be outlined in the clinical trial agreement that should be signed prior to site initiation.

11.6 Funding

This trial is being funded by a grant from the Chief Scientist Office (CSO), Grant Reference TCS/18/08. Some site payments are available and full details of these are documented in the site agreement.

11.7 Protocol Amendments

Any change to the trial protocol will require an amendment. Any proposed, non-administrative, protocol amendments will be initiated by the CI following discussion with the TMG and any required amendment forms will be submitted to the regulatory authority, ethics committee and sponsor(s). The CI and the TMG will liaise with trial sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and sponsor representative. Before the amended protocol can be implemented favourable approval must be sought from the original reviewing REC, trial Sponsor, HRA (English sites only) and participating site R&D offices.

11.8 Allocation of Trial Responsibilities

11.8.1 Sponsor Responsibilities (NHS GG&C)

The Sponsor is responsible for confirming there are proper arrangements for the initiation and management of the trial. Any Sponsor's responsibilities that have been delegated to the CI will be documented within the 'Responsibilities delegated to the Chief Investigator' form. The duties will be performed via the CRUK CTU as the co-ordinating centre for the trial.

11.8.2 Chief Investigator (CI)

The CI is directly responsible for:

- Ensuring the protocol and any amendments are in place.
- Clinical oversight of the safety of trial participants, including the ongoing review of the risk/benefit.
- For review of SAEs and determination if SAEs meet the criteria for expedited reporting within 24 hours.
- Providing advice on medical issues that arise involving trial participants.

At the outset of the trial development period, the CI will sign the CRUK CTU Memorandum of Understanding (MoU) document which details the key responsibilities of the CI and CRUK CTU, where applicable giving indicative timelines for completion. In addition, the CI will sign the Sponsor Responsibilities Agreement. From the perspective of the Sponsor and for ethics purposes, the CI for the trial will be Dr Kevin Blyth.

11.8.3 CRUK Clinical Trials Unit (CTU)

The CRUK CTU delivers the overall management of the clinical trial. This includes, but is not limited to, all regulatory submissions (ethics, HRA, and R&D) and any amendments, all administration relating to the submissions and any amendments, circulation of all correspondence to participating sites, data management, monitoring of data quality and safety, ongoing communication with participating sites, management of safety reporting, and where applicable the management of any financial arrangements.

11.8.4 Participating Site

The Participating Site is solely responsible for the management of the trial within their site. This includes ensuring local management approval has been given, ensuring the trial is conducted according to GCP requirements, and ensuring the appropriate insurance or indemnity is in place. The Participating Site is also responsible for arranging access for on-site monitoring and auditing as identified in the trial protocol and also for regulatory inspections.

11.8.5 Principal Investigator (PI)

The PI is responsible for:

- The delegation of trial activities within their site and ensuring all personnel are adequately trained and qualified to carry out their responsibilities.
- Providing evidence of GCP training (usually a certificate) or undergo the required GCP training.
- The safety and wellbeing of trial patients,
- Reporting any deviations from the protocol to CRUK CTU Glasgow

  Reporting SAEs or safety issues within 24 hours of becoming aware of the event, including using medical judgement in assigning seriousness causality and expectedness

Full details of the responsibilities of the PI are outlined in the Clinical Trial Agreement. Two original copies of this will be held – one with the Sponsor and the other at the participating site. A photocopy of the signed agreement will also be held at the coordinating trial office.

12 QUALITY ASSURANCE

12.1 Audits and Inspections

Trial Investigators must permit trial related monitoring, audits, REC review and regulatory inspections as required, by providing direct access to source data, CRFs and other documents (patient medical records, investigator site file, and other pertinent data). The trial may be subject to inspection and audit by NHS Greater

Glasgow and Clyde as Sponsor, the CRUK CTU, to ensure adherence to GCP. If an inspection is scheduled at any participating site, the site must notify the Sponsor at the earliest opportunity. It is the sponsor's responsibility to inform the investigator(s) of all intended audits and regulatory inspections involving the participating site. It is the investigator's responsibility to ensure appropriate resources at site and that the inspector(s) have access to all source data.

12.2 Protocol Non-compliance

Protocol non-compliances must be reported by the site study team to the CRUK CTU as soon as they are identified. Non-compliances may also be identified by the Clinical Trial Monitor, and the site staff and CRUK CTU staff will work together to complete a protocol deviation form and put corrective and preventive actions in place to avoid repeated non-compliance. Where the deviation is of a more serious nature, the Sponsor may be required to report a serious breach of protocol to the Ethics Committee. The Sponsor reserves the right to suspend recruitment at a site until an investigation has taken place and corrective and preventive measures have been put in place to ensure future patient safety and/or data integrity.

14 PUBLICATION POLICY

The STRATIFY TMG is responsible for approving the content and dissemination of all publications, abstracts and presentations arising from the trial and for assuring the confidentiality and integrity of the trial. It will provide collaborators the International Committee of Medical Journal Editors (ICMJE) criteria http://www.icmje.org/icmje-recommendations.pdf) will be used to ensure all those who have contributed to the study are appropriately acknowledged. No site or individual will publish data without prior approval of the TMG. The data arising from STRATIFY will belong to the trial Sponsor, NHS Greater Glasgow and Clyde. The TMG shall act as custodian of this data.

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