SPOTLight

The Severn Pleural Disease Outcomes: Long-term Insights study

Chief Investigator (CI)

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Signature page

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the study in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the study publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the study will be given; and that any discrepancies and serious breaches of GCP from the study as planned in this protocol will be explained.

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Signature:

..... Date: ...../...../.....

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Contents

List of abbreviations

APR	Annual Progress Report
CRP	C-reactive protein
CT	Computed tomography
CXR	Chest X-Ray
DAL	Digital air leak
eCRF	Electronic case report form
EQ-5D-5L	EuroQol 5D Health Questionnaire
FBC	Full blood count
GCP	Good Clinical Practice
ICD	Intercostal chest drain
IPC	Indwelling pleural catheter
ISF	Investigator Site File
LAT	Local anaesthetic thoracoscopy
LDH	Lactate dehydrogenase
LFTs	Liver function tests
MTA	Material Transfer Agreement
MHRA	Medicines and Healthcare Products Regulatory Authority
NBT	North Bristol NHS Trust
PIS	Participant information sheet
PPI	Patient and public involvement
PROM	Patient reported outcome measures
PS	Performance status
R&D	Research and Development
REC	Research Ethics Committee
SOP	Standard Operating Procedure
TMF	Trial Management File
TUS	Thoracic Ultrasound Scan
U&E	Urea & electrolytes
VAS	Visual Analogue Scale

Study summary

Study title	The Severn Pleural Disease Outcomes: Long-term Insights Study
Short title	SPOTLight
Study design	Longitudinal observational cohort study
Study participants	Patients with pleural disease referred to the pleural service at North Bristol NHS Trust
Planned recruitment rate	100 patients/year minimum
Planned study period	5 years
Study objectives	To improve understanding of long-term, patient-reported and objective clinical outcomes in pleural disease and provide a platform for the evaluation of current and future physiological, biochemical, and radiological biomarkers in the diagnosis and management of patients with pleural disease
Inclusion criteria	1. Confirmed presence (radiologically) of either: a. pleural effusion OR b. pleural thickening, not solely attributable to pleural plaques OR c. spontaneous primary or secondary pneumothorax 2. Patient normally lives within the catchment area of the Bristol hospitals or within reach of NBT and is unlikely to relocate within 12 months 3. Age 16 or over 4. Has access to telephone and/or internet
Exclusion criteria	1. Previously enrolled in SPOTLight 2. Patient (or appropriate proxy) not able to provide written informed consent 3. Patient is in the final stages of life or sufficiently frail to make study involvement inappropriate

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The Sponsor and Funders have no role or remit in the study design, conduct, data analysis and interpretation, manuscript writing or dissemination of results.

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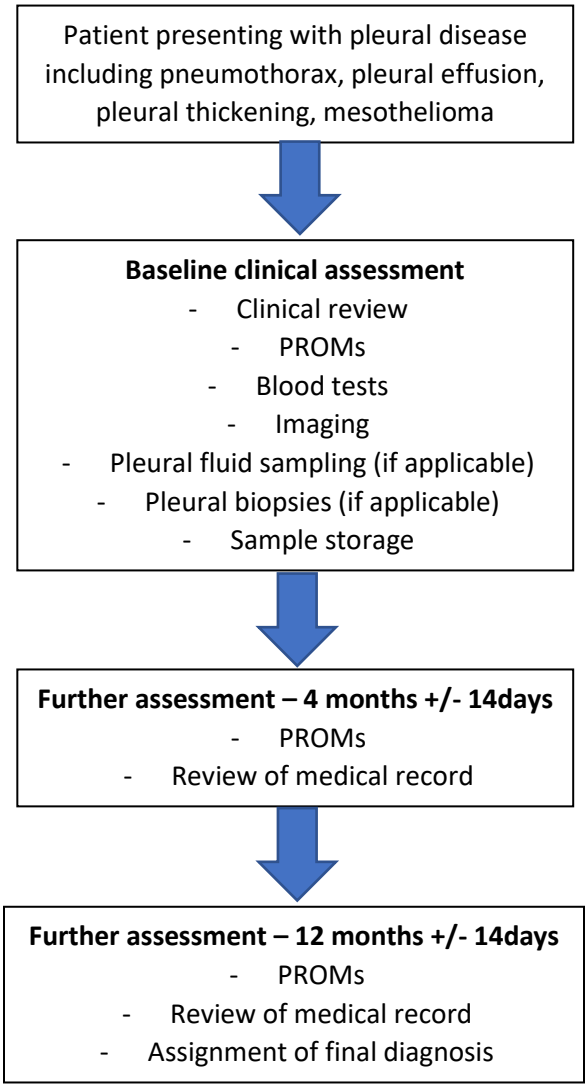
Study flow chart:



Plain English summary

The pleural membranes are two thin layers of tissue which cover the outside of the lungs. The pleura are vulnerable to many different diseases. These include:

1) Pleural effusions – this is where the pleura become inflamed, leading to excess fluid build-up in the space between the lung and the chest wall (the pleural space).
2) Pleural cancer – this kind of cancer is called mesothelioma and is usually associated with exposure to asbestos.
3) Pleural thickening – this is where the lining around the lung can become scarred and thickened, often because it has been inflamed in the past, either due to infection, a previous effusion, medications, or other underlying medical conditions.
4) Pneumothorax – this is where air becomes trapped in the pleural space causing the lung to collapse, sometimes due to a leak of air from the lung itself or following an injury to the chest wall (either accidental or due a medical/surgical procedure).

All these conditions can cause breathlessness, which can be severe and distressing for patients. Unfortunately, a general lack of research means there are many unanswered questions when choosing how to best diagnose and manage pleural diseases. There is often no single test that can provide us with a diagnosis, and patients frequently need multiple procedures, both to help diagnose their condition and to manage their symptoms.

We therefore plan to create a new, long-term study to collect data on patients with all these types of pleural disease, so that we can better understand how to diagnose and manage their condition, and the impact their symptoms and their diagnostic and management pathway have on their quality of life.

We will do this by inviting every patient who attends Southmead hospital with a pleural condition to take part in a simple follow-up study. We hope to involve at least 600 over 5 years and when further funding is confirmed to extend this to at least 1200 people over 10 years. We will ask participants for permission to record data about their health, and to store small amounts of blood, fluid & tissue for future laboratory tests, if these samples are obtained as part of routine care of their condition. We can then use these samples to apply more cutting-edge tests as they become available, which may improve our ability to diagnose the underlying cause of pleural disease. This study would not require any additional visits to hospital as we would only collect information about what happens to them during their usual care. We would also ask patients to fill out brief questionnaires about how they are affected by their condition.

We also want to encourage patient involvement with new patient support groups, which we can then ask to help us design our future studies and communications with patients, ensuring we always reflect patients' priorities in our research, and to help spread the word about what we find.

Scientific abstract

Pleural disease represents a significant burden on healthcare, with an estimated 360 per 100,000 people being diagnosed with pleural disease annually.(1) Despite this, there has been far less research in this area compared to other, rarer respiratory diseases until recently, and far fewer advances in management.(2)

Pleural effusions

Pleural effusion is the most common manifestation of pleural disease, with 1.5 million people developing effusions annually in the US.(3) The differential diagnosis is broad; the commonest causes include infection, malignancy and heart failure (4), but differentiating between these causes can be challenging. An estimated 12.5% of non-malignant pleural effusions are attributed to an idiopathic pleuritis or unknown cause.(5) Management of pleural effusions varies significantly depending on the underlying cause, therefore swift and accurate diagnosis is paramount with some causes requiring urgent or immediate management.

There currently are no specific tests that confirm the underlying cause of a pleural effusion. The clinical picture in conjunction with biochemical, cytological and radiographic findings will then guide further tests, for example a pleural biopsy.

The initial step determines whether the effusion is a transudate or an exudate using Light's Criteria, although these criteria have not been updated in over 30 years.(6) Within these categories the differential remains extensive, and the criteria are not infallible. It is well-recognised that 20-25% of transudative effusions related to congestive cardiac failure are misclassified as exudates(7), as a result of which patients may be required to undergo further unnecessary investigations, or that up to 5% of malignant effusions can be transudative.(8)

The overall diagnostic sensitivity of pleural fluid cytology for malignancy is approximately 60%(9), but in some cancers, such as mesothelioma, diagnostic yield can be as low as 6% from pleural fluid(10) These patients may then require further invasive diagnostic tests to confirm a cause for their effusion.

Differential cell counts in pleural fluid can help narrow the differential diagnosis of an effusion but are not in themselves diagnostic. Neutrophilic effusions are more commonly found in acute pathology, whilst lymphocytic effusions usually indicate a degree of chronicity, such as malignancy and cardiac effusions(11), but the cell differential offers little beyond these generalisations. The above demonstrates that, currently, pleural fluid testing is only able to modify the likelihood of a diagnosis rather than provide a diagnosis

For these reasons, there is a drive to seek novel diagnostic tests that may streamline the diagnostic pathway in patients with pleural effusions and enable us to better differentiate between the underlying cause of effusions. Recent research has been directed towards the evaluation of genetic material (genomics or transcriptomics), proteins (proteomics) & small molecules (metabolomics) to identify novel biomarkers that could differentiate between benign and malignant aetiologies. These studies show

promise, but are frequently limited by small data sets and further analysis in larger cohorts is required.(12–15)

In addition to the diagnostic challenges, pleural effusion is a condition with a high symptom burden. Patients with effusions often require multiple hospital admissions or attendances and multiple invasive procedures. In malignant disease, effusions are associated with a far poorer prognosis than other sites of metastatic disease, with a median life expectancy of 4-9 months.(16) During this time, maintaining patient's quality of life and reducing the need for repeated invasive procedures should be a priority.

By collecting data on the patient experience, we aim to better understand our patients' experience of their disease and the impact of its investigation and management on their quality of life. Novel diagnostic and prognostic biomarkers that can predict patient outcomes, need for intervention and response to treatment could help clinicians to manage patients' expectations about their disease and make informed, patient-centred treatment decisions.

Mesothelioma

Mesothelioma is a rare cancer affecting the serosal surfaces, primarily the pleura. More rarely, the pericardium or peritoneum can be affected. There is a strong association with previous asbestos exposure, and despite increasing regulation and prohibition of asbestos production and use, global incidence has continued to rise. Due to a long latency period between asbestos exposure and development of mesothelioma, patients are often diagnosed late in life. (17) A diagnosis of mesothelioma confers a poor prognosis, with a median survival of 9.5 months.(17) Only 7% of patients survive to 3 years.(18)

Diagnosis can be challenging, given the low diagnostic yield of cytology(10) and the propensity of mesothelioma to imitate other epithelial or sarcomatoid malignancies, and many patients require multiple invasive pleural procedures to reach a diagnosis. Current clinical guidelines require a histological diagnosis based on the presence of mesothelial markers and the absence of adenocarcinoma markers on immunohistochemistry(17), but in some cases this is not possible, either due to patient frailty or wishes precluding a biopsy, there being no viable biopsy target or biopsy yielding inconclusive immunohistochemistry results. In the absence of a histological diagnosis, a consensus clinical decision is sometimes made based on clinical history, radiological and cytological investigations.

There is no cure for mesothelioma; the available chemotherapy regimes have only been shown to extend prognosis by 2-3 months and only 40% of patients will respond to chemotherapy.(19,20) The addition of Bevacizumab to a Carboplatin-Pemetrexed regime has been demonstrated to improve survival rates to a median of 19 (16-22) months.(21) Unfortunately, given the demographics of this patient cohort and the high symptom burden associated with mesothelioma, many patients are not fit enough to tolerate chemotherapy, and those that do may suffer significant side effects without any meaningful benefit in terms of increasing life expectancy.

For the same reasons, research in this cohort can be challenging. Many patients with mesothelioma would not be eligible to take part in clinical trials, due to their poor performance status, leading to a

disparity between trial and real-world populations. In addition, the significant symptom burden associated with the disease may make some patients unwilling to become involved in research.

Further research is required in this area to identify new biomarkers that may both enable mesothelioma to be diagnosed more rapidly and less invasively and help us understand which patients are most likely to benefit from treatment. This, alongside an improved understanding of the impact of patient's disease and our interventions on quality of life, could enable us to make more patient-centred decisions in a cohort where maintaining quality of life is a priority.

Pleural thickening

Pleural thickening, in which the parietal or visceral pleura becomes fibrosed, can have a range of both benign and malignant causes, including prior asbestos exposure, infection, previous chest trauma, connective tissue disease, benign pleural tumours, medications and either primary or metastatic disease affecting the pleura. This thickening may be seen in association with a pleural effusion, or as an independent finding. Many patients are asymptomatic, but extensive thickening can cause a restrictive defect on pulmonary function testing and patients may present with breathlessness, cough or chest pain.

Computed tomography (CT) scanning is the primary radiological modality for assessing pleural thickening. Although there are specific features that are highly specific for malignancy, such as circumferential thickening, nodularity, mediastinal involvement and invasion of the chest wall, one or more of these signs is only seen in 40-55% of patients with malignant aetiology.(22) As such, these patients often require further investigation, either with a different modality of scan, interval scanning over time or with more invasive investigations to obtain a tissue biopsy. A biopsy can be taken under CT or ultrasound guidance, should there be a site amenable to biopsy. For patients in whom there is no clear biopsy target, more invasive techniques, such as medical thoracoscopy or surgery may be required which, in the absence of pleural fluid, conveys a higher risk of complications.

There are currently no clear guidelines in the UK regarding how patients with pleural thickening should be investigated and monitored. The most recent British Thoracic Society (BTS) guidelines, currently undergoing public review, advise monitoring with follow-up imaging in those without a histological diagnosis, but do not advise a duration for which to do this.(23) Improving our knowledge of the proportion of patients presenting with unexplained pleural thickening who progress to mesothelioma, and within what timeframe, could help guide monitoring and management in the future.

Pneumothorax

Spontaneous pneumothorax is a common condition, with over 9,000 hospital admissions relating to pneumothorax recorded in the UK in 2016. The risk of recurrence is also high, estimated at 25% within 5 years of first presentation.(24) There remains controversy about how, when and for whom intervention is required, largely due to a lack of high-quality evidence. British Thoracic Society (BTS) guidelines provide clear advice on different treatment strategies for primary (PSP) and secondary (SSP) spontaneous pneumothorax(25), but compliance with these guidelines amongst non-respiratory

healthcare professionals is reportedly only 20-40%.(26) For this reason, further research to provide robust evidence on which to base these guidelines is required.

The BTS guidelines advocate a more conservative approach in patients with primary spontaneous pneumothorax, particularly if small or the patient is not breathless. A recent randomized controlled trial to compare conservative management with intervention in moderate to large pneumothoraces showed promising results, but was limited by selection bias, small sample size and participant attrition.(27)

There is significantly less evidence available regarding the management of secondary pneumothoraces, and a stark disparity between trial and real-world populations. Due to the increased rate of recurrence following aspiration (60% vs 25% in PSP)(28), guidelines recommend the insertion of a small-bore chest drain in this cohort.(25) There have been limited further studies into less invasive methods of managing SSP, and those that have been carried out have been limited by small recruitment numbers.(29)

The development of new technology could drastically improve disease understanding and patient outcomes in pneumothorax. Over the last 10 years the use of digital devices to measure and monitor air leak following cardiothoracic surgery has increased, and has been demonstrated to improve consistency regarding chest drain removal post-operatively(30) and to reduce duration of chest tube drainage and hospital admission.(31) Whilst the use of digital devices to measure air leak in medical patients with spontaneous pneumothorax is becoming more commonplace, the evidence is limited to small prospective and pilot studies.(32)

With our study, we will be able to collect real-world data on the incidence rates, demographics and outcomes for patients in this, until recently, under-researched cohort, and evaluate how the use of novel devices to assess air leak and manage these patients in an ambulatory setting can influence their treatment and outcomes.

Aims & Objectives:

Overall aims

The aims of this prospective cohort study are to provide platforms for:

1) The improvement in understanding of long-term, patient-reported and objective clinical outcomes in pleural disease, and
2) The evaluation of current and future physiological, biochemical, and radiological biomarkers in the diagnosis and management of patients with pleural disease

It is likely that the number and type of questions which will be addressed by this project will evolve (with ethical approval) in response to both continual broader scientific advances and knowledge, and to the findings generated by SPOTLight itself.

Not all research questions will be applicable to all patients who are enrolled in the study due to the differences in pleural conditions.

Research questions which may be addressed as part of the study are listed below.

1. Clinical outcomes

1.1 What is the average survival for patients with pleural disease?
1.2 What is the average number of interventions required to confirm the presence/absence of malignant pleural disease?
1.3 Which factors predict survival and/or progression in patients with pleural disease?
1.4 What is the recurrence rate in patients treated for pneumothorax?
1.5 What is the incidence of complications following common pleural procedures?
1.6 Which factors pre-dispose to the presence/development of non-expandable lung?
1.7 Which factors pre-dispose to the presence/development of pleural fluid septation and loculation?
1.8 Which factors pre-dispose to the need for intrapleural therapy and/or surgery for pleural infection?
1.9 Which factors pre-dispose to successful/unsuccessful pleurodesis?
1.10 Which factors influence the development, and rate and volume of pleural fluid production?
1.11 What are the healthcare costs associated with managing pleural disease?
1.12 Can pressure auto-sensing drainage devices be used to improve the time to pleurodesis, and the patient experience, in those requiring recurrent drainage?

2. Patient-reported outcomes

2.1 How does a patient's self-reported quality of life vary following diagnosis with pleural disease?
2.2 How does a patient's self-reported quality of life vary in line with the management strategy for their pleural disease?
2.3 Can Visual Analogue Scale (VAS) score for breathlessness predict clinical outcomes in patients with pleural disease?
2.4 Can Visual Analogue Scale (VAS) score for pain predict clinical outcomes in patients with pleural disease?
2.5 Which alterations can be made to current practice to improve the patient experience of pleural procedures?
2.6 Do existing respiratory, palliative care, and cancer quality of life/symptom burden measures have a role in the management of patients with progressive pleural disease?

3. Biological biomarkers

3.1 Can metabolomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.2 Can proteomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.3 Can transcriptomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.4 Can genomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?

3.5 Can epigenomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.6 Can metagenomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.7 Can exosomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.8 Can lipidomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.9 Can glycomic methods be applied to identify new biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?
3.10 Can existing laboratory or point-of-care tests, including enzyme-linked immunosorbent assays (ELISA), be applied to identify (or improve) biomarkers or scoring systems for use in the diagnosis, prognosis and/or management of pleural disease?
3.11 Can histopathological and cytological methods be applied to identify or improve biomarkers for use in the diagnosis, prognosis and/or management of pleural disease?

4. Physiological biomarkers

4.1 In patients with spontaneous pneumothorax, how does digital air-leak measurement correlate with clinical outcomes?
4.2 Can real-time pleural pressure measurement be used to predict clinical outcomes in pleural disease?
4.3 Can clinical markers/scores of general frailty be applied to patients with pleural disease?
4.4 Can lung function tests be used to predict clinical outcomes in pleural disease?
4.5 Can exercise capacity be used to predict clinical outcomes in pleural disease?
4.6 Can measured and/or reported activity levels be used to predict clinical outcomes in pleural disease?

5. Radiological biomarkers

5.1 Can assessment of chest radiographs be used to predict outcomes in spontaneous pneumothorax?
5.2 Can thoracic ultrasound be used to predict clinical outcomes in pleural disease?
5.3 Can novel radiological software (e.g., artificial intelligence software) be applied to routinely acquired images to improve diagnostics and guide management of pleural disease?
5.4 What are the relative diagnostic rates of the imaging modalities used in pleural disease?
5.5 Does the use of intra-pleural contrast improve the diagnostic capabilities of standard imaging techniques?

Methodology

Study design

SPOTLight is a prospective, longitudinal cohort study of patients diagnosed with pleural disease.

Following the success of other studies(33), we will employ an adaptive design to enable us to keep pace with evolving evidence. As new areas of interest, data collection tools, or scientific techniques emerge, we will assess their suitability for inclusion in the study and update our protocol and study documentation with a view to assessing their role in the diagnosis, management, and outcome of patients with pleural disease. Such inclusions may be incorporated into the existing SPOTLight framework or may take the form of dedicated sub-studies.

Where necessary, depending on the specific pleural disease area of interest, patients will be provided with supplemental information and/or asked to complete supplemental consent regarding additional tests or sub-studies.

Study setting

SPOTLight is a single-centre study, recruiting from patients presenting to North Bristol NHS Trust (NBT).

Participant eligibility criteria

Inclusion criteria:

To be eligible to participate in the cohort, patients must meet all the following criteria:

1. Confirmed presence (radiologically) of either:
   a. pleural effusion OR
   b. pleural thickening, not solely attributable to pleural plaques OR
   c. spontaneous primary or secondary pneumothorax
2. Patient normally lives within the catchment area of the Bristol hospitals or within reach of NBT and is unlikely to relocate within 12 months
3. Age 16 or over
4. Has access to telephone and/or internet

Exclusion criteria:

To be eligible to participate in the cohort, none of the following criteria should apply:

1. Previously enrolled in SPOTLight
2. Patient (or appropriate proxy) not able to provide written informed consent
3. Patient is in the final stages of life or sufficiently frail to make study involvement inappropriate

Study Procedures

Recruitment

The recruitment target is a minimum of 100 patients per year, with no defined maximum enrolment.

The SPOTLight study is funded for 5 years with a view to extending for a further 5 years (contingent upon securing additional funding if required).

Given the observational nature of this study, patients will be eligible to co-enrol in other studies if invited.

Identification and screening

Potential participants will be identified, for example, from the emergency department, the acute medical unit, inpatient wards and outpatient clinics at North Bristol NHS Trust (NBT). In parallel with their routine clinical review by the NBT Pleural Service, which will include radiological tests such as thoracic ultrasound and chest X-ray, they will undergo assessment for inclusion in SPOTLight by a study team member. Those meeting the eligibility criteria described above will be invited to discuss the study with a member of the research team. They will be provided with a participant information sheet (PIS) and given sufficient time to read it (in their own opinion). Where possible, this PIS will be sent out to the patient in advance of their clinic appointment. The patient will then be given an opportunity to ask any questions and, if willing to proceed, will be invited to give written, informed consent to enrol.

Participation in SPOTLight will not impact on any part of patients' routine care and they will be entitled to withdraw from the study at any point, without giving a reason.

Patients will have to have undergone relevant medical investigations to meet the inclusion and exclusion criteria, specifically radiographic imaging (e.g. TUS, CXR or CT scan) to confirm presence of pleural effusion/thickening or pneumothorax. These are not study specific procedures but are performed as part of the participants' routine clinical care.

Consent

Informed consent will be sought for patients to allow their baseline and follow up clinical and radiological data, and for any biological samples obtained as part of routine clinical practice or this study to be used to help address the research questions above. Individuals receiving consent will be authorized, trained and competent to participate according to the protocol, principles of Good Clinical Practice (GCP) and Declaration of Helsinki.

No additional procedures are required as part of the SPOTLight study. However, as per standard practice, informed consent will be sought for procedures carried out as part of the patient's routine care and investigation.

Patients will be made aware that their samples and data will likely be used to address a number of current and future research questions, and that this may involve their information and samples being shared with external collaborating research organisations. Patients will, however, be given the option to exclude particular kinds of their data from being used.

Participation in future studies and/or patient groups

At the time of enrolment, patients will be approached to provide their contact details. As well as facilitating collection of SPOTLight follow-up data, patients will be asked if these details may be used to approach them, if suitable, for:

1. Inclusion in future studies which may be undertaken by either North Bristol NHS Trust or the University of Bristol Academic Respiratory Unit, and/or
2. Inclusion in focus group meetings relating to studies in development or ongoing, and/or
3. Inclusion in patient/public involvement (PPI) activities relating to studies in development or ongoing, and/or
4. Participation in clinical support/patient groups related to their illness

Consent for such participation, if received, will be valid for the duration of ethical approval for the SPOTLight study, unless the patient withdraws consent.

Prior to contacting a participant for potential involvement in any of the above, study staff will be required to check whether the patient remains alive or if they have moved outside of the study area.

Patients who are unable to provide consent for themselves

A proportion of adult patients who present to hospital with pleural disease will not be capable of providing informed written consent to participate in a research study. This may be a temporary (e.g. delirium in the context of acute infection / sepsis) or long-standing (e.g. cognitive impairment in the context of dementia) state. It is important to consider enrolling these patients into this study since there is evidence that a confused state (whether acute or chronic) has a negative prognostic impact on clinical outcomes.(34,35) Not including confused patients in this study may therefore introduce unintentional bias. When enrolling a patient lacking capacity into the study, legislation in relation to the participation of such individuals in clinical research must be followed.

All adults presenting with pleural disease should be helped as far as possible to be involved in the decision of whether to participate in the study, even where the research team deems them to not have capacity to give consent for themselves. This process should involve both verbal discussion and the provision of written information about the study.

If a patient is unable to give informed, written consent for themselves, the research team will identify and seek an opinion of a “consultee” to advise about the potential participant’s wishes in relation to whether to be involved in the study, considering the patient’s past and present wishes. Individuals who may act as a consultee for a patient unable to provide consent are outlined below:

1. A personal consultee – this should be an individual who cares for or has an interest in the patient’s welfare but is not receiving financial remuneration or fulfilling a professional role. This could be, for example, a family member, carer or friend; an attorney acting under a Lasting Power of Attorney; or a court-appointed deputy with pre-existing knowledge of the person prior to their appointment as deputy.

2. A nominated consultee – in situations where a personal consultee cannot be identified or is not willing or able to fulfil the role, the research team may wish to identify a "nominated consultee". This should be an individual with no connection with the research project, who is willing to be consulted about the participation of the person lacking capacity in the study. This could be an individual with a professional relationship with the person, for example, regular paid carers of the patient e.g., care home staff or nurses, the individual's solicitor, or general practitioner.

If the consultee is willing to approve the participation of the person lacking capacity in the study, they will be asked to sign a consultee declaration form to this effect.

When samples of blood, fluid or tissue are collected as part of the participant's routine clinical care, additional samples will be collected for research purposes. The consultee can withdraw consent for this if they feel it is appropriate and only clinical data will be collected from this participant; no study specific samples (e.g., blood and pleural fluid) would be collected from these individuals.

If a participant enrolled in the study at a time when they were unable to provide informed, written consent themselves subsequently regains capacity, informed, written consent should be sought to continue being a part of the study.

If a participant who had previously consented to participate subsequently loses capacity, their consent should be assumed to continue in the first instance. A consultee should be approached by the study team as soon as possible to seek their advice and agreement that the previously signed consent form remains valid. A consultee declaration form should be completed where appropriate.

Further guidance on the process of identifying a consultee for research involving adults who lack capacity to consent is available in a Department of Health publication "Guidance on nominating a consultee for research involving adults who lack capacity to consent", published in 2008.

Additional consent provisions for the collection and use of participant data and biological specimens in sub-studies

In the event that a potential participant is eligible to participate in a sub-study running at the time of their initial enrolment, they will be provided with an additional, sub-study specific, PIS and consent form. This is essential to maintaining the adaptive design of our study and will enable us to provide patients with the additional information and consent form for a relevant sub-study simply and concisely, without the need to change the standard PIS and consent form. This ensures that patients only need to provide consent for involvement in studies that will be relevant to them, rather than incorporating all sub-studies into the same PIS and consent form.

Follow-up schedule

Unless necessary for specific research questions or sub-studies, all participants will only undergo assessment immediately following study consent ("baseline assessment"). At 4- and 12-months, patients will be contacted to complete further questionnaires as detailed below. Patients will be asked to agree to being contacted if follow-up is missed.

Clinical data will be acquired from the medical records at 4-months and 12-months post enrolment.

To minimise the impact on participants, any sub-studies requiring additional face-to-face visits will be ideally have them scheduled to coincide with existing clinical or research study appointments.

Data collection

Baseline assessment

Clinical information

The baseline assessment for all patients will incorporate routinely collected clinical information, such as:

- History and examination by a Respiratory physician, including duration of symptoms, co-morbidities and past medical history, current/recent medications, smoking status including cannabis, asbestos and other inhalational exposures, frailty score and performance status (PS).
- Chest X-Ray (CXR)
- Standard blood tests (such as full blood count and renal function)
- Thoracic ultrasound scan (TUS)
- Diagnostic aspirate results (such as protein levels and pH)
- Digital air leak (DAL) measurement in the case of pneumothorax.
- Computed tomography (CT)

Biological research samples

For patients who undergo a pleural aspiration at baseline or a later date, a maximum of 30mls of additional blood and 50mls of additional pleural fluid (if applicable) will be collected for research purposes. If a patient has had a blood test performed prior to the research team discussing the study with them, an additional blood test may be performed for research purposes.

For patients who undergo a pleural biopsy procedure following enrolment, a maximum of 2 additional tissue samples (per procedure) may be obtained and retained for research purposes, if felt clinically appropriate to do so by the operator.

Where necessary (e.g., in the event of a non-diagnostic biopsy sample), any research samples obtained and stored as part of the SPOTLight study may be retrieved for routine clinical analysis if thought to be beneficial to the participant's ongoing clinical care.

All samples will be processed according to the latest Standard Operating Procedures (SOP) before being transferred to an appropriate cold-storage facility for long term storage. An electronic tissue log will be maintained.

Patients will be asked to provide consent for the use of biological research samples by the study team (or collaborating organisations engaged and approved by the study team), either at the time of sampling or in the future, for ethically or clinically approved tests. They will be made aware that their samples may be transferred off North Bristol NHS Trust premises to facilitate the undertaking of such tests. A Material Transfer Agreement will be completed for any and all transfers of samples to external sites for storage and/or analysis.

Patient-reported outcome measures

Standard Patient Reported Outcome Measures (PROMs) will be collected from all participants.

These will include:

- Visual Analogue Scale (VAS) for breathlessness & pain
- EuroQol 5D Health Questionnaire (EQ-5D-5L)

Where necessary, additional PROMS relevant to specific research questions may also be collected during the baseline assessment.

Further study assessments

4 months post-enrolment (+/- 14 days)

Clinical information

A member of the study team will review the participant's clinical records (local, regional, and national) to collect data on key clinical outcomes, including but not limited to:

- Working diagnosis
- Number and type of clinical encounters including inpatient admissions, length of stay, outpatient clinic reviews and day case procedures
- Number of type of interventions, including diagnostic and therapeutic aspirations, intercostal chest drain (ICD) insertions, intra-pleural fibrinolytic administration, indwelling pleural catheter (IPC) insertions and removals, local anaesthetic thoracoscopy (LAT) and surgical procedures.
- Complications of procedures
- Mortality

Patient-reported outcome measures

Participants will be asked to complete the same PROMs as during the baseline assessment. These may be completed:

- Face-to-face, if attending the hospital for another reason
- Via email, if having consented to being contacted this way
- Over the telephone with the assistance of a research team member, if having consented to being contacted this way.

12 months post-enrolment (+/- 14 days)

Clinical information

A member of the study team will review the participant's clinical records (local, regional, and national) to collect data on key clinical outcomes, including but not limited to:

- Diagnosis given by the clinician undertaking follow-up
- Number and type of clinical encounters including inpatient admissions, length of stay, outpatient clinic reviews and day case procedures

- Number of type of interventions, including diagnostic and therapeutic aspirations, intercostal chest drain (ICD) insertions, intra-pleural fibrinolytic administration, indwelling pleural catheter (IPC) insertions and removals, local anaesthetic thoracoscopy (LAT) and surgical procedures.
- Complications of procedures
- Mortality

To ratify the reason for the participant's initial presentation, an additional pleural specialist will review the clinical record and assign a final diagnosis based upon the clinical information acquired over the previous 12 months and with reference to standardised diagnostic criteria outlined in a separate SOP. In the event of disagreement between the diagnosis given by the clinician during follow up and the additional pleural specialist, the case will be discussed with a third pleural specialist and an agreement reached.

Patient-reported outcome measures

Participants will be asked to complete the same PROMs as during the baseline assessment and at the 4-month time point. These may be completed:

- Face-to-face, if attending the hospital for another reason
- Via email, if having consented to being contacted this way
- Over the telephone with the assistance of a research team member, if having consented to being contacted this way.

Schedule of assessments:

Description	Investigation	Baseline assessment	4-month follow up assessment	12-month follow up assessment
Clinical review	Patient demographics	X		
	Disease history	X		
	Patient co-morbidities	X		
	Assessment of PS	X		
	Medication history	X		
	Pleural intervention history	X	X	X
	Complications/Recurrence	X	X	X
	Diagnosis	X	X	X
	Mortality	X	X	X
PROMs	Breathlessness VAS	X	X	X
	Chest pain VAS	X	X	X
	EQ-5D-5L QoL score	X	X	X
	Additional PROMs relevant to specific research questions	X^	X^	X^
Blood tests	FBC	X*		
	U&E	X*		
	LFT	X*		
	CRP	X*		
	LDH	X*		
	Total protein	X*		
	Additional tests	X*		
Imaging	TUS	X*		
	CXR	X*		
	CT	X*		
	Additional imaging relevant to specific research questions	X*		
Pleural fluid analysis	pH	X^		
	LDH	X^		
	Total protein	X^		
	Glucose	X^		
	Microscopy, culture & sensitivity	X^		
	Cytology	X^		
	Additional tests	X*		
Additional tests	Digital assessment of air leak	X^		
	Pulmonary function testing	X*		
	Patient activity levels	X^		
Pleural biopsies	Histology	X*		
Storage of samples	Blood sample for storage	X		
	Pleural fluid sample for storage	X^		
X = REQUIRED	X* = IF CLINICALLY INDICATED		X^ = IF APPLICABLE	

Withdrawal criteria and loss-to-follow up

Withdrawal of subjects

All patients will provide written consent to sample collection, storage and analysis where required and to study follow up. Participants have the right to withdraw from the study at any time, without justification. This will not affect their further or on-going care.

If a participant withdraws from the study, any reason(s) given will be recorded in the eCRF, alongside the nature of withdrawal, as outlined below:

Patients may choose to withdraw consent to:

- All study involvement, including the use of data and samples already collected and further data collection. Samples and follow-up data already collected will be destroyed in line with Trust policy.
- Further study involvement, including follow-up visits and data collection. Consent is maintained for data and samples already collected, which may be stored and analysed.
- Data collection, including further follow-up visits, and the use of clinical data already collected. Consent is maintained for blood and fluid samples already collected, which may be stored and analysed.
- Sample storage and analysis, and for any data already obtained from these samples. Samples and their associated data will be destroyed in line with local policy. Consent is maintained for further follow up and data collection.

Any data already used in published reports cannot be withdrawn.

Loss to follow-up

Loss to follow-up will be minimised by careful liaison between the participants and the study team. Follow-up can be undertaken in the most convenient manner for the patient, whether this is in person at an existing appointment, by telephone or by email. If a patient moves away, follow-up could be undertaken remotely. Any participants lost to follow-up will be recorded in the participant withdrawal/loss to follow-up form.

Statistical considerations

Sample size calculation

The prospective nature of this observational study renders a sample size calculation unnecessary. Our aim is to recruit a minimum of 100 patients per year. Over the 5-year period for which the study is initally funded, this would allow us to adequately assess a range of the above research questions. After 5 years, contingent upon securing further funding as necessary, we will seek an extension to continue to address the outstanding clinical questions in addition to novel areas of interests in the form of future sub-studies.

Analyses

As the SPOTLight study will address a variety of research questions, and will utilise a wide range of scientific techniques, it is not practical to describe analysis methods in the protocol.

Where appropriate, a statistical analysis plan will be prepared and carried out based upon the specific requirements of individual research questions or sub-studies. The study team may choose to conduct analyses using the assistance of (or by outsourcing to) external collaborators with expertise in specific methods, topics, or analysis techniques.

Data Management

Data collection tools and source document identification

Source data will be largely electronic from NHS Trust computer systems i.e., patients' medical records, laboratory, and radiology reports.

Any data which does not already exist and is being recorded for the first time will be collected and stored in the Investigator Site File (ISF) and if clinically appropriate, patients' medical records. Data will be collected on either paper CRFs i.e., patient reported outcome measures, clinical history sheets, or if appropriate, directly entered onto an eCRF which can be downloaded and stored in patients' medical records as source data.

Data handling and record keeping

Data entry at each study visit will use a bespoke study database housed on the UOB server, built using the validated open-source REDCap system and regularly backed up. A member of the study team will facilitate data capture and entry into the database via an electronic case report form (eCRF) with the support of the clinical team. Each participant will be allocated an unambiguous subject identification code (study participant ID).

REDCap includes data validation checks which are inbuilt into the database build and a data query management system to allow management of data quality throughout the study. The SPOTLight database will be validated as part of the Database Activation process and final data quality checks will be incorporated as part of the Database Lock process.

It is also possible to download the data for all records in this project in a single PDF file that could be printed and retained with the Trial Management File (TMF). This file contains the actual page format as you would see it on the data entry page or survey and includes all data for all records for all data collection instruments.

Access to Data, Data Protection and Confidentiality

All data will be stored in line with Good Clinical Practice (GCP) requirements and the General Data Protection Regulation (GDPR).

All study documentation will be kept secure in an access restricted environment and only accessible by SPOTLight study staff and authorised representatives from the Sponsor and regulatory authorities to permit study-related monitoring, audits and inspection.

Patient data will be kept confidential. On all study specific documents, the patient will be referred to only by the study participant ID. The recruitment log stored on NBT computers will contain identifiable patient information to enable the research team to link participants to their records on clinical data systems. Identifiable information will only be accessible to SPOTLight study staff and in situations where consent has been granted for a specific purpose i.e., consent to be contacted about future studies.

No study information will be routinely shared with any external third parties. For the purposes of specific analyses, linked anonymised data will be shared. Only data required for each specific analysis will be shared. Any data being shared externally will be transferred securely electronically with password protection.

REDCap is password protected with only approved users having access. User access can be restricted to different levels by assigning users with limited permissions based on their role (i.e., data entry only). Interaction with the software automatically creates an access log data trail, ensuring that the access of data can be audited to ensure data protection (e.g., by data point, function or individual user).

Archiving

Once all required downloads have been confirmed with the NBT REDCap team, they will delete the study data from the REDCap project but keep the metadata and put this into archived status. This way, the project can still be brought back to life if needed (by uploading the data from long term storage) but it no longer exists on the REDCap server. Data will be retained as per NBT archiving policy. With participants' consent, anonymised/pseudo-anonymised electronic research data will be stored indefinitely and made available for future analysis.

Ethical considerations

Research Ethics Committee (REC) review and reports

Prior to the study commencing, approval will be sought from a REC for the study protocol, informed consent forms and other relevant documents, for example, patient information sheets (PIS) and GP information letters and supplemental information sheets and/or consent forms required for specific research questions. Substantial amendments that require review by the REC will not be implemented until the REC grants a favourable opinion for the study. Any amendments will be reviewed and accepted by the Medicines and Healthcare Products Regulatory Agency (MHRA) and/or NHS Research and Development (R&D) where necessary.

All correspondence with the REC will be retained in the Study Master File/Investigator Site File. An annual progress report (APR) will be produced by the Chief Investigator and submitted to the REC within 30 days of the anniversary date on which the study was approved. The Chief Investigator will notify the REC at the end of the study.

Peer review

This study has undergone thorough external peer review throughout its development. Peer reviewers have a broad expertise and experience appropriate to the scale of the study.

Patient and Public Involvement

Patients with experience of pleural disease have been involved in the development of this study, both in terms of development of the concept and by providing feedback on all patient-facing documentation. We have discussed the purpose of the study with a variety of our current patients, who agree this is a worthwhile project.

We also plan to use this project to increased patient involvement by developing patient support groups for different pleural diseases and involving patients in the design of future sub-studies, larger studies and patient communications.

Regulatory Compliance

SPOTLight will not commence until a favourable REC opinion is obtained.

Protocol Compliance

Prospective, planned deviations from the protocol are not allowed and must not be used.

Accidental protocol deviations should be adequately documented on the relevant forms and reported to the CI and Sponsor as appropriate.

Frequently recurring deviations from the protocol are not acceptable, require immediate action and could be classified as a serious breach if the safety, physical or mental integrity of the participants or the scientific value of the study is affected. In the event of a serious breach, the Sponsor will be notified immediately. The Sponsor will then notify the licensing authority in writing.

Finance and Insurance

The study has been funded by Southmead Hospital Charity, an unrestricted research grant provided by Rocket Medical and some research infrastructure funding provided by the NIHR Biomedical Research Council.

Insurance will be provided by the Sponsor, North Bristol NHS Trust.

Amendments

Relevant approvals for each sub-study will be sought via specific study amendments. Where appropriate, additional requirements and data collection needs will be included as separate sub-studies in appendices. As not all sub-studies will be relevant to every patient, a sub-study specific Patient Information Sheet and Consent form will be provided that is designed as an add-on to the core Patient Information provided and Consent already received.

Reporting and Dissemination

A specific dissemination plan will be devised for each individual question as it is studied and a full report prepared on completion of the study.

Appendices

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Amendment tracker

Standard Operating Procedures

Archiving SOP RI QMS SOP 010 - Archiving.pdf (nbt.nhs.uk)