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North Bristol NHS Trust

Oxford Respiratory Trials Unit
University of Oxford

Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry

TAPPS trial

Protocol

A randomised, open-label trial to determine the most effective method for the management of malignant pleural effusions in patients with a good performance status.

Chief Investigator	**Dr Nick Maskell**
Trial Sponsor	**North Bristol NHS Trust**
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Date: 05/12/2014

SIGNATURE

GENERAL INFORMATION

This document describes the TAPPS trial and provides information about procedures for patients participating in it. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its creation, but corrections or amendments may be necessary. Clinical problems relating to this study should be referred to the relevant chief or principal investigator, or the trial co-ordinator, whose details can be found below.

COMPLIANCE

The trial will be conducted in compliance with the protocol, Research Governance Framework, Data Protection Act and other guidelines as appropriate.

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SECTION 1 – ABSTRACT AND TRIAL DESIGN

1.1 Abstract

Malignant pleural effusions (MPE) are a major cause of morbidity amongst cancer patients, usually leading to significant breathlessness. Currently, there are about 250,000 new cases per year in the United States and the UK, which causes a heavy burden on healthcare services. Median survival from diagnosis is typically only around 6 months.

Management of malignant pleural effusions usually entails attempted pleurodesis. The most proven and widely-used sclerosant is sterile talc, which may be given using one of two methods. The first, more traditional approach is to remove the fluid using a bedside intercostal chest drain and to then instil a talc slurry solution through it. An alternative is to perform a local anaesthetic (medical) thoracoscopy and to spray a powder ('poudrage') under direct vision of the pleural surfaces.

Thoracoscopy is becoming more widely available in the UK and is used frequently to perform talc poudrage. Our own audit data has suggested a benefit to using this approach over bedside talc slurry, although the published trials in this area have been few and have suffered from methodological flaws. There are also potential benefits in patients' quality of life, and costs to healthcare providers in using poudrage, as this procedure involves a much shorter hospital stay (1-2 days vs. 5-7 days for slurry [1]).

The TAPPS trial aims to answer definitively whether there are significant differences in efficacy, safety and cost in using thoracoscopy and talc poudrage over talc slurry pleurodesis for the management of malignant pleural effusions. We aim to recruit 330 patients from across the UK and randomise them to receive either talc poudrage (intervention) or bedside talc slurry (control), and to then compare pleurodesis success rates at three months. This trial has the potential to inform and change current NHS and international practice by determining the most effective approach to managing this difficult group of patients.

1.2 Lay summary

Patients who suffer with cancer (malignancy) can sometimes develop fluid (an effusion) in between the two tissue layers which surround the lung (the pleura). These malignant pleural effusions, or MPE, can be a major cause of disabling symptoms, especially breathlessness, as the build-up of fluid can compress the lung and prevent it from expanding. Virtually any cancer can lead to an effusion, but the commonest causes are those involving the lung and the breast.

The simplest method for managing malignant pleural effusions is to insert a small chest tube under local anaesthetic, allowing the fluid to drain away. However, it is extremely common for fluid to re-accumulate over time after the drain is removed. In order to prevent this, an irritant substance, usually talc powder in the form of a slurry (powder mixed with water but not dissolved), is injected into the chest tube before it is removed. This aims to cause the pleura to stick together, which prevents any further fluid build-up. This is known as pleurodesis and when attempted using talc slurry in this way is

successful about 80% of the time on average [2]. This method can, however, be burdensome to patients, who often have to remain in hospital for up to a week.

In an increasing number of centres in the UK it is now possible for patients to undergo a minor operation to allow doctors to examine the pleura directly. This is called a thoracoscopy and can also usually be done using only local anaesthetic. A fibre-optic camera is passed in to the pleural space through a small hole in the chest wall, which then allows for a more detailed examination of the pleura as well as for immediate and rapid drainage of fluid. If a malignant pleural effusion is suspected, pleurodesis can be attempted during the operation by spraying a fine talc powder over the whole of the affected lung, using the camera to ensure an even spread. This approach is known as "poudrage." Patients are left with a chest drain in place for a day or two before being discharged home.

Thoracoscopy and poudrage are considered by some to be the superior method for inducing a pleurodesis in MPE, as it may be more effective and therefore result in less fluid recurrence, which in turn may also result in reduced cost as patients require a shorter hospital stay and are less likely to be re-admitted after discharge. However, the few large trials which have attempted to address this question directly have had methodological flaws and have therefore not resulted in a wide scale change in practice.

The aim of the TAPPS trial is to determine whether talc slurry or poudrage at thoracoscopy is superior for the management of malignant pleural effusions in patients who are otherwise relatively fit. We aim to recruit 330 patients from around the UK to receive either standard talc slurry treatment or poudrage, and assess whether there are differences in the proportion of patients in each group who have failed pleurodesis at 3 months. This trial aims to establish best practice for patients and will thus have the potential to influence practice in the management of MPE both nationally and internationally.

1.3 Study design

1.3.1 Trial type

Multi-centre, open-label randomised controlled trial to determine whether local anaesthetic thoracoscopy and talc poudrage is a more effective method of pleurodesis than traditional inpatient chest drain insertion and subsequent talc slurry instillation.

1.3.2 Disease and patient group studied

Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT), through routine inpatient reviews, and through outpatient clinic appointments. Patients will be screened using the inclusion and exclusion criteria (see section 3.2). Eligible patients will be invited to participate on a consecutive basis. Participation in the trial will be discussed with the patient at the appropriate routine outpatient appointment. They will be allowed sufficient time to fully consider trial entry. Full written, informed consent will be obtained prior to enrolment.

1.3.3 Randomisation

Patients will be randomised following admission to hospital for their trial procedure. Randomisation will be performed using a central telephone service (see page 7).

Eligible patients will be randomly assigned in a 1:1 ratio using minimisation with a random element to undergo either chest drain insertion with talc slurry pleurodesis or thoracoscopy with talc poudrage. The day of randomisation is defined as Day 0.

Minimisation will be performed by Sealed Envelope Randomisation Services (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA).

The minimisation factors are:

- Type of underlying malignant disease (mesothelioma; lung cancer; breast cancer; other)
- WHO / ECOG performance status (0 or 1; 2 or 3)

Patients should have their allocated procedure within 24 hours of admission, but ideally this should be on the same day, immediately after randomisation.

1.3.4 Outcome measures

Primary endpoint

The primary endpoint is the number of patients who experience pleurodesis failure up to three months (90 days) post randomisation.

Secondary endpoints

1. The number of patients with pleurodesis failure up to 30 days post randomisation.
2. The number of patients with pleurodesis failure up to 180 days post randomisation.
3. Requirement for further pleural procedures up to 180 days post randomisation, based on an independent, blinded assessment
4. Percentage radiographic (chest x-ray) pleural opacification at the 1-month, 3-month and 6-month post randomisation follow-up visits, and after initial drain removal.
5. Self-reported health-related quality of life at the 1-month, 3-month and 6-month follow-up post-randomisation visits, as measured using the SF-36 and EQ-5D questionnaires.
6. Self-reported thoracic pain and breathlessness at 7 days post procedure, and 30, 90 and 180 days post randomisation, measured using visual-analogue scale (VAS) scores.
7. All-cause mortality up to 180 days post randomisation
8. Time to pleurodesis failure, censored at 180 days post randomisation.
9. Number of nights spent as a hospital inpatient up to 90 days post randomisation, including length of initial stay

1.3.5 Trial duration

Patient involvement in study follow-up will last until death or 6 months post randomisation, whichever is sooner. Patients will have trial follow-up appointments at 1, 3 and 6 months post randomisation. Trial participants' mortality data beyond 6 months may be collected using the NHS central register, as long as separate consent for this is given. The study end date is January 31st 2017.

1.3.6 Investigational product

Sterile medical talc, in the context of the TAPPS trial, is not considered to be an investigational medicinal product (IMP).

1.3.7 Trial centres

This trial will recruit initially from multiple NHS hospitals in England. All of the hospitals involved have a successful track record of recruiting to pleural clinical trials. The lead centres will be North Bristol and Oxford, with the trial being co-ordinated by a clinical research fellow based at Southmead Hospital in Bristol and a trial manager based at the Oxford Respiratory Trials Unit. They will be responsible for trial setup, delivery, liaison and query resolution at the other sites.

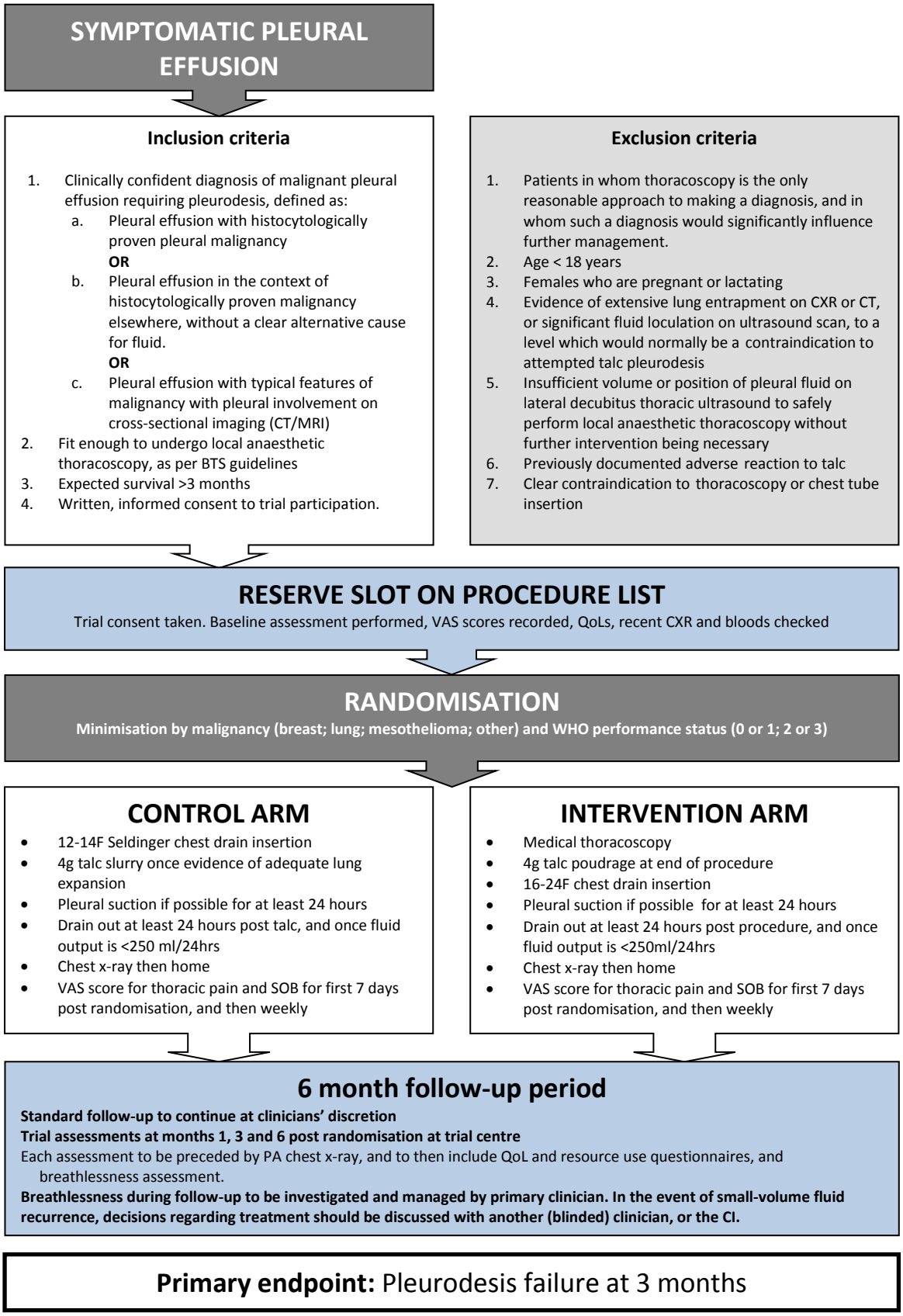
1.3.8 Trial sponsor

The study is sponsored by North Bristol NHS Trust, who will oversee and ensure the compliance and integrity of the trial.

1.3.9 Trial funding

The TAPPS trial is supported by a grant from the NIHR Health Technology Assessment (HTA) programme.

1.4 Trial flow chart



SECTION 2 – BACKGROUND

2.1 Scientific summary

Pleural effusions are a common complication of many cancers, with symptoms often requiring intervention. Data from 10 years ago suggests there are up to 175,000 new cases of malignant pleural effusion (MPE) in the USA per year and around 40,000 per year in the UK [3], although these figures may now be conservative as the global burden of malignancy continues to rise each year, and with it the incidence of MPE. Recent figures suggest the age-standardised incidence of all-cause malignancy in the UK to be around 386 cases per 100,000 per year. Projections suggest this rate will remain stable in the UK, but this equates to over 130,000 new cases of cancer per year by the year 2030 once population increase is accounted for [4]. Additionally, as people diagnosed with malignancy continue to live longer, the number of cases of MPE will inevitably rise also.

Although over 90% of patients with malignant pleural mesothelioma may go on to develop MPE [5], this disease accounts for only a small percentage of the burden of MPE. The incidence of mesothelioma is projected to peak around 2020, with an expected age-standardised rate of around 7.5 cases per 100,000 [4]. The majority of cases of MPE are associated with cancer elsewhere in the body [2], meaning the presence of an effusion typically indicates metastatic disease. The commonest cause in both sexes is lung cancer (37.5%), followed by breast cancer in women (16.8%), and lymphoma [2]. By 2030 in the UK, the incidence of lung cancer in men is expected to fall by around 7%, but this is likely to be negated by an identical percentage rise in the female population and an overall rise in the number of cases, all of which will have a significant impact on the incidence of MPE [4].

The aetiology of these effusions may be complex and multifactorial. Malignant processes can cause direct micro- or macro lymphatic obstruction which disrupts pleural fluid drainage, while at the same time vascular disruption and increased capillary and pleural permeability will tend to cause fluid to accumulate in the pleural space [6]. Since these mechanisms are often unchecked by treatment, MPEs have a tendency to be large in volume and recurrent in nature. In fact, massive effusions, in which there is complete or near-complete opacification of the hemi-thorax are rarely caused by anything other than malignancy [7].

The majority of patients with MPE will therefore be symptomatic at presentation, usually experiencing breathlessness and chest discomfort [2]. The mechanism for breathlessness due to an effusion may be as varied as the underlying cause, but often includes a combination of diaphragmatic impairment and reduced pleural compliance [8]. In those with MPE, these symptoms may also be accompanied and exacerbated by effects due to the underlying tumour, and patients often complain of non-specific symptoms such as general malaise and weight loss [2]. Such a combination of symptoms can have a significant effect on the performance status of patients, which may impact on overall survival [9] and which may in turn influence future treatment options for the underlying disease. However, since the primary source of a MPE may be of diverse origin, previous studies have had difficulty in reliably predicting an individual's survival based upon its presence alone. Various attempts have been made to group causes together, and these have shown median survival following diagnosis to be around 4

months [10], although this has approached 2 years in some series [11]. There have been attempts to try and predict survival based upon various patient, fluid or disease characteristics, but there has been no prospective study specifically addressing this issue. In general it is perceived that those who survive the longest are those who have a better response to systemic therapy for the underlying condition.

Given the above, there exists a rationale for early and definitive management of malignant pleural effusions, especially as removal of as little as 250-500 mls of fluid can have a significant impact on diaphragmatic mechanics and thus on breathlessness and functional status. While fluid can often be aspirated using a simple needle and syringe, this method does not address fluid recurrence, and many patients would require repeated thoracenteses if this was relied upon alone. Indeed, this approach to effusion management may only be seen as appropriate in those considered too frail for any other intervention, or who may be seen as having a short life expectancy [2]. Indwelling pleural catheters may be an alternative for the management of MPE for some patients, and they have been shown to be a viable option for outpatient management for many [12]. They can also induce pleurodesis (see later), which potentially solves the problem of fluid recurrence in the longer term, although rates of this occurring are often low, typically being around 50% [13,14] overall and lower in lung malignancy. In addition, IPCs require community services which can accommodate regular home drainage and specialist expertise for their insertion. Another potential drawback to their use is the length of time they need to stay in place to be effective, which can extend to many weeks or months, making them potentially less economical than other, more traditional methods [15].

A large proportion of patients who have a MPE will not have a cancer diagnosis at initial presentation, and will often require therapeutic and diagnostic pathways to occur simultaneously. Perhaps the most efficient way of achieving this is to perform a thoracoscopy, whereby direct visual examination of the pleura allows targeted biopsies to take place, following rapid drainage of the effusion using low-pressure suction [16]. Thoracoscopy has traditionally been the domain of surgeons, but in recent years has begun to be performed under local anaesthetic and sedation by physicians (local anaesthetic thoracoscopy; LAT). In those centres which do not have ready access thoracoscopy, which remains the majority, drainage of large volumes of pleural fluid is classically managed with intercostal tube insertion as a first step. Following this, cytological results may be used to confirm or refute the diagnosis of malignant pleural effusion, although diagnostic rates of around 60%, at best, are inferior to those of biopsy [17–19]. Despite it only being possible to definitively identify an effusion as malignant with pleural histological or cytological evidence, fluid collections are often classified as MPE based on initial radiological and / or direct visual (thoracoscopic) appearances. This approach allows the issue of probable fluid recurrence to be addressed immediately after symptomatic drainage.

Pleurodesis is the adherence of the visceral and parietal pleura, which causes an obliteration of the pleural space. It may be induced by the introduction of an irritant substance which causes a localised inflammatory reaction and subsequent fibrin deposition. Removing the pleural space reduces the possibility of pleural fluid build-up, which means induction of pleurodesis is considered the mainstay of treatment for recurrent malignant pleural effusions. Many substances have been shown to induce

chemical pleurodesis although by far the most commonly used in the West is talc, which has been shown to be superior to alternatives such as tetracycline or bleomycin [20].

Talc is predominantly hydrated magnesium silicate and has been used for the purposes of pleurodesis since the 1930s [21] . For many years ungraded talc was used but this was associated with instances of severe inflammatory response, both systemically and locally [22,23], which was later confirmed experimentally. Subsequent evidence has however shown that large-particle, sterile talc can be both safe and effective if used in doses up to 4 grams [24], and this is now the standard for chemical pleurodesis across much of the United Kingdom. The now widespread use of large-particle talc has meant the side effects of pleurodesis tend to be minor, the commonest being fever, pain and gastrointestinal upset [20,25,26], although there have been rare cases of empyema [27]. For this reason the routine use of sterile technique and appropriate analgesia, including premedication with intrapleural lidocaine, is recommended when attempting talc pleurodesis [2]. It should also be noted that, in those with malignant pleural effusions, there has been no documented increase in mortality by the use of talc pleurodesis over the use of either alternative agents or chest drains alone [20].

Overall pleurodesis success rates are typically high with talc, ranging from 81% to 100% [2], although this efficacy may vary considerably in real-world practice due to differences between clinicians and individual centres. The traditional method to instil talc, the control arm in this study, requires a patient to be admitted for chest tube insertion and fluid drainage. The size of chest drain which should be inserted has historically been the matter of some debate, with larger tubes (24-32 French) being advocated as less likely to become obstructed following sclerosant instillation. However, randomised trials have shown no difference in pleurodesis efficacy between large and small bore (10-14 French) tubes [28–30], with less discomfort being experienced by those patients with small drains [31]. Following admission, drain insertion and fluid drainage, a chest x-ray is performed to assess the degree of lung expansion. Complete expansion is used as a surrogate for pleural 'dryness' and is felt to represent the ideal time to instil sclerosant [2]. Talc is administered in slurry form and is made up with a physiologically inert fluid such as 0.9% saline. Drains are removed once subsequent drainage volumes become low, potentially indicating successful pleurodesis. The whole process typically requires an inpatient stay of 5-7 days [1], often with at least 24 hours of pleural suction. This may have significant health economic impacts as well as the potential to impair the quality of life of patients with more limited life spans.

An alternative to this traditional approach is the application of sterile talc powder under direct vision at thoracoscopy (insufflation, or poudrage). This has potential advantages in that it allows patients to be diagnosed and treated in a single sitting, which minimises time in hospital, as well as reducing the number of pleural interventions which are required overall. The latter point is especially relevant in patients with malignant mesothelioma, who are particularly prone to procedure tract seeding [32,33]. However, despite an increasing number of hospitals having access to medical thoracoscopy, it is still much less ubiquitous than Seldinger drain insertion, with the requirement for specialist training and the increased costs of the procedure being major limitations, along with the more complex nature of the procedure. This means patients must be of a better performance status if they are to be considered for LAT [16] which potentially limits its generalisability over chest drain insertion. Furthermore, at the end of a thoracoscopy

patients must have a large-bore chest drain left in-situ to allow the lung to re-expand – the larger minimum for drain gauge being determined by the size of the thoracoscopy port used – which has the potential, as discussed above, to cause increased discomfort.

The efficacy of talc poudrage at 1 month for pleurodesis has been documented in a number of studies. Published success rates tend to lie around 85%, although there is significant heterogeneity between study groups which limits reliability. However, combined data from the only two randomised trials suggests a much lower pleurodesis rate at 67% [16]. Direct comparison of talc slurry and talc poudrage was within the scope of the 2004 Cochrane review which, along with suggesting talc was the most efficacious sclerosant, found talc poudrage at thoracoscopy to have an improved relative risk of non-recurrence (1.19) over talc slurry [20] . A subsequent large randomised trial by Dresler, published in 2005, suggested there was only a trend towards superiority of poudrage (p=0.1), with no significant overall difference between the two methods. Theoretically, the inclusion of patients with trapped lung, whereby the visceral and parietal pleura are unable to appose, will inevitably lead to reduced rates of pleurodesis. This was borne out in sub-group analysis which not only saw a rise in pleurodesis success once these patients were excluded, but also the emergence of a significant difference between poudrage (82%) and slurry (71%), with p=0.045. Further stratification by disease sub-type revealed a clinically important 45% decrease in pleurodesis failure with thoracoscopy in good performance status patients with lung or breast cancer (thoracoscopy 18% failure versus tube 33%, p=0.02), with no benefit in frailer patients. Although there remains the suggestion from this study that poudrage is superior to slurry, there are significant conduct and methodology flaws which limit the interpretation and applicability of its data [34]. A further large, European, but non-randomised series showed talc poudrage also had fewer failures than talc slurry (12% vs 31%). However, this study did not use the clinically relevant outcome of the frequency of later repeated pleural drainage, and did not study non-malignant causes of recurrent pleural effusion. The study population also differed from UK practice, most notably in the lack of mesothelioma patients and with a large proportion of gastrointestinal malignancies [35].

In summary, although there is good evidence for the use of LAT in the diagnosis of MPE, the role of talc poudrage for the induction of pleurodesis and the prevention of fluid recurrence remains unclear. Chest drain insertion with talc slurry is universally available, less expensive and relatively easy to perform, but may have a significantly poorer success rate and may result in longer hospital stays. The TAPPS trial aims to definitively resolve the question of whether talc poudrage is a superior method for the induction of pleurodesis in MPE, allowing clinicians to make the most appropriate and best informed decisions and recommendations to patients.

2.2 Research questions

2.2.1 Primary research question

For patients with a confirmed malignant pleural effusion and good performance status:

1. Does thoracoscopy and talc poudrage increase the proportion of patients with successful pleurodesis at three months post-procedure, when compared to standard therapy with chest drain insertion and talc slurry instillation?

2.2.2 Secondary research questions

1. Does thoracoscopy and talc poudrage reduce the time to pleurodesis failure, measured at three and six months post-procedure, when compared to standard therapy with chest drain insertion and talc slurry instillation?

2. Does fluid drainage and talc poudrage at thoracoscopy improve chest x-ray appearances after initial drain removal, and at 1, 3 and 6 months post randomisation, when compared to standard fluid drainage via chest tube alone?

3. Does thoracoscopy and talc poudrage cause less breathlessness and thoracic pain for the first seven days post procedure, when compared to standard therapy with chest drain insertion and talc slurry instillation?

4. Does thoracoscopy and talc poudrage improve health-related quality of life over the six months post randomisation, when compared to standard therapy with chest drain insertion and talc slurry instillation?

5. Is thoracoscopy and talc poudrage cost effective over six months, when compared to standard therapy with chest drain insertion and talc slurry instillation?

6. Does thoracoscopy and talc poudrage reduce healthcare utilisation during the six months post randomisation, when compared to standard therapy with chest drain insertion and talc slurry instillation?

SECTION 3 – PATIENT SELECTION

3.1 Setting

Recruitment will take place from NHS hospitals around the UK over a 24 month period. Each centre will have an interest in pleural disease management, with the majority expected to perform in excess of 80 attempted pleurodeses per year. The trial is supported by the appropriate local and regional cancer networks.

Clinical care, trial follow-up, imaging, thoracoscopy and poudrage, and drain insertion and slurry administration will be provided by medical professionals at patients' base trial hospitals or appropriate satellite centres. Further care will be provided by ward and specialist nurses in these centres, who will also be available for telephone support. Patients will complete self-assessed scores for breathlessness and thoracic pain in hospital initially, but subsequently in their own homes. The specifics of follow-up are detailed in section 4.2.10.

3.2 Enrolment criteria

3.2.1 Inclusion criteria

1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis, defined as:
   a. Pleural effusion with histocytologically proven pleural malignancy, OR
   b. Pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid, **OR**
   c. Pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging (CT/MRI), without a clear alternative cause for fluid.
2. Fit enough to undergo local anaesthetic thoracoscopy
3. Expected survival >3 months
4. Written, informed consent to trial participation

3.2.2 Exclusion criteria

1. Patients in whom thoracoscopy is the only reasonable approach to making a diagnosis, and in whom such a diagnosis would significantly influence further management.
2. Age < 18 years
3. Females who are pregnant or lactating
4. Evidence of extensive lung entrapment on CXR or CT, or significant fluid loculation on ultrasound scan, to a level which would normally be a contraindication to attempted talc pleurodesis
5. Insufficient volume or position of pleural fluid on lateral decubitus thoracic ultrasound to safely perform local anaesthetic thoracoscopy without further intervention being necessary
6. Previously documented adverse reaction to talc
7. Clear contraindication to thoracoscopy or chest tube insertion

3.3 Co-enrolment guidelines

Patients may only be enrolled in the TAPPS trial once. For the duration of their trial involvement they should not be entered into any other clinical trial which attempts to directly affect pleural fluid production, management or drainage. Oncological management of the underlying disease will be guided by the site-specific cancer MDTs, and any treatments or entry into relevant systemic anti-cancer trials will not be restricted. Should a participant be considered for co-enrolment in another trial of any other origin then liaison with the TAPPS trial team is essential to ensure compatibility between the trial protocols.

3.4 Screening and recruitment

This trial is to recruit in an open-label manner, with both the patient and the trial team members aware of a participant's treatment arm, because the potential trial interventions are dissimilar in terms of method. As it could not be considered safe or ethical to undertake 'dummy' procedures, any attempt at patient blinding is considered impractical.

It is anticipated that there will be significant overlap between the physicians carrying out trial interventions, and those carrying out trial follow-up assessments. For this reason, it is also considered impractical to attempt to keep trial team members blind to treatment arm.

The recruitment target is 330. The statistical justification for this is given in section 6.2 and in the statistical analysis plan Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT), at routine outpatients' appointments, and during inpatient reviews. Patients will be screened using the inclusion / exclusion criteria as above. Screening logs documenting reasons for exclusions will be kept throughout the trial. In addition to the exclusion criteria, for the purposes of screening, any patient in whom trial participation would be inappropriate (as determined by the local investigator) should not be enrolled in the trial. This should be clearly documented on the screening log. Screening and recruitment will be performed by local trial medical and nursing staff.

Eligible patients will be invited to participate on a consecutive basis, and will be provided with an information leaflet at the earliest opportunity. Participation in the trial will be discussed with the patient by a medical or nursing member of the local trial team. They will be allowed sufficient time to fully consider trial entry, as well as to ask questions of investigators. Full written, informed consent will be obtained prior to enrolment.

3.5 Bias reduction

Due to the open-label nature of this trial, the potential for introducing bias into data collection and analysis is inherently greater than if the trial were performed in a fully blind fashion. For the reasons described above this trial cannot be performed ethically or safely in a blinded manner. Therefore, in order to minimise the possibility of bias in the primary outcome, the decision to undertake further pleural intervention in patients who develop breathlessness and have a small-volume recurrent effusion will be discussed

with a blinded assessor. As a secondary analysis, two independent parties, blinded to treatment group and subsequent clinical course, will assess the need for further pleural intervention in all patients.

SECTION 4 – ASSESSMENT AND TREATMENT OF PATIENTS

4.1 Standard care

All patients should normally be discussed, or should have been discussed, in their local thoracic MDT, or, if the underlying malignancy is not pulmonary, an appropriate specialist MDT. Mesothelioma patients should be discussed at a regional MDT if available. For all issues other than those pertaining to the drainage and management of the malignant pleural effusion, treatment discretion lies with the primary physician, surgeon or team.

Normal clinical review during the trial period will take place in the usual outpatient or inpatient setting, and will typically be carried out by oncologists or respiratory physicians. The frequency of clinical review will depend on patient choice, severity of symptoms and clinical discretion. In general, patients who are managed with chemotherapy for underlying malignancy are typically reviewed every 2-3 months.

All attempts should be made to co-ordinate trial follow-ups with routine clinical follow-up appointments or inpatient periods. Patients should be given contact details for an appropriate specialist nurse at the earliest opportunity, as per standard local practice.

4.2 Trial interventions

4.2.1 Pre-enrolment

Patients will be identified for potential trial participation following discussion at the appropriate cancer MDT, at routine clinic appointments, or during inpatient review, as described above. All patients will fall into one of two categories: those with a confirmed malignant pleural effusion based on a pleural histocytological diagnosis; or those with an effusion and the strong suspicion of malignant pleural involvement, based on radiological appearances or the presence of a histocytologically proven malignancy elsewhere. These patients should be reviewed as normal with a view to discussing further treatment options for their effusion.

Patients must be considered fit enough to potentially undergo local anaesthetic thoracoscopy (as per the British Thoracic Society guidelines 2010), and should be WHO / ECOG performance status 3 or better at the time of enrolment, with no evidence of ventilatory failure. If the patient is not theoretically averse to trial participation, then a patient information sheet regarding the TAPPS trial should be provided, with sufficient time allowed for the patient to fully consider trial entry. Contact details for an appropriate specialist cancer nurse should also be provided if not already given. Patients may require a therapeutic thoracocentesis in order to transiently improve symptoms, especially in the case of larger volumes being present. The volume of fluid removed during therapeutic aspiration should not be limiting to later trial-related procedures.

Patients should then be allocated a place on a dedicated thoracic procedure list and a date given for admission to hospital to coincide with this, if they are not already an inpatient.

4.2.2 Consent

Trial consent may be taken up to seven days prior to the baseline assessment being performed, although it is recommended that they occur as close together as possible. If, by the end of the seventh day after the consent form is signed, the baseline assessment has not taken place, the patient should be asked to sign a new consent form.

Patients should be made aware that, if they consent to trial participation, during their slot on the procedure list they will undergo either a thoracoscopy and poudrage, or Seldinger chest drain insertion with slurry later. Whichever treatment arm they are allocated to will entail a stay in hospital. If they are not willing to participate in the trial, then decisions regarding their further treatment will continue to lie with their normal primary physician, surgeon or oncologist. Patients' further care will not be affected by the decision not to participate. **Those patients who remain amenable should have written consent for trial participation taken.**

In addition, if the patient is amenable, consent should be taken for genetic sample analysis alongside consent to trial participation. Refusal to sign this second consent will not affect a patient's treatment or trial procedures.

Once the treatment arm has been allocated following randomisation, standard consent for either medical thoracoscopy and poudrage, or chest drain insertion and slurry, should also be taken as per local policy.

4.2.3 Enrolment procedure

The <u>recommended</u> procedure for outpatient enrolment involves admission to hospital, trial consent, trial baseline assessment and randomisation, and the allocated trial procedure all taking place within a 24 hour window (see Appendix 1).

If greater flexibility is required, patients may undergo their allocated procedure at any time up to the end of the third day following their baseline assessment and randomisation. So, for example, if a patient is consented, assessed and randomised on a Friday morning, they must undergo their allocated procedure by the end of the following Monday.

For inpatients, the baseline assessment and randomisation should take place within 7 days of trial consent being obtained. The allocated trial procedure should take place before the end of the third day post randomisation. It may be more convenient, however, for patients who are given the PIS as an inpatient to have a therapeutic aspiration to facilitate rapid discharge. This then allows patients to be managed more flexibly as outpatients.

4.2.4 Baseline assessment

All patients who consent to trial entry should be admitted to an appropriate clinical area prior to their intervention. A baseline assessment should be performed by a member of the trial team and documented on the appropriate case report form (CRF). Much of this information may already be available from recent consultations and will include:

- Relevant medical history and physical examination, to include;
    - Onset and nature of symptoms
    - Type of malignancy causing effusion (if known)
    - Pleural procedures to date
    - Current ECOG / WHO performance status
    - Current analgesia history
- Visual-Analogue Scale (VAS) score to assess thoracic pain and breathlessness
- Quality of life assessment using SF-36 and EQ-5D health questionnaires
- Blood test results from within the last 10 days
- Thoracic ultrasound scan results

- In those participants in whom it is appropriate, trial blood samples should also be taken (see section 4.2.8)

If the patient has a correctable clotting abnormality, then this must be corrected to locally acceptable standards before any intervention can be considered. The reason(s) for any delays should be clearly documented in the patient notes.

4.2.5 Randomisation

Randomisation should occur immediately after the patient undergoes their baseline assessment.

Randomisation will be performed using a central telephone service (see page 7).

Eligible patients will be randomly assigned in a 1:1 ratio using minimisation with a random element to undergo either chest drain insertion with talc slurry pleurodesis or thoracoscopy with talc poudrage. The day of randomisation is defined as Day 0.

Minimisation will be performed by Sealed Envelope Randomisation Services (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA).

The minimisation factors are:

- Type of underlying malignant disease (mesothelioma; lung cancer; breast cancer; other)
- WHO / ECOG performance status (0 or 1; 2 or 3)

Randomisation should occur as close as possible to the start of the procedure list.

If randomisation or an allocated procedure occurs outside of the above windows then a protocol deviation should be reported.

4.2.6 Post randomisation

Once treatment arm is known, patients should undergo the procedure to which they have been allocated. Patients should have their allocated procedure before the end of

the third day after their baseline assessment and randomisation, but should ideally have it performed as close to randomisation as possible.

Trial procedures should be carried out in a standard fashion using the appropriate trial specific procedure (TSP) document. TSPs for both drain insertion with talc slurry instillation, and thoracoscopy with poudrage are provided and should be followed.

4.2.7 Control (talc slurry) arm

Patients should have a small-bore (12-14 French) chest drain inserted under strict aseptic conditions, using Seldinger technique, with appropriate local anaesthesia and pre-medication as necessary. As per normal clinical practice, written consent specific to drain placement should be obtained, and a suitable site for drain placement should be identified using contemporaneous ultrasound. Insertion guide marks made in another fashion (e.g. 'X' mark in radiology department) should not be relied upon. Drains should only be inserted by persons of adequate training and experience. Documentation in the patient notes should include the details of the operator; the size of the drain inserted; the number of sutures used; and the dose and strength of all medications given. In those patients at North Bristol and Oxford who have consented to trial samples being taken, pleural fluid samples should also be taken, processed and sent as necessary(see section 4.2.10).

A chest x-ray (ideally posterior-anterior) should be performed between 18 and 24 hours after drain insertion to assess for pleural opacification and trapped lung. If there is no evidence of trapped lung or significant fluid, as determined by the patient's primary physician, then the patient should have talc slurry instilled through the chest drain, following the appropriate TSP.

Patients who continue to have evidence of significant pleural opacification may need to undergo further imaging to confirm the cause. If the significant component of the opacification is felt to be due to pleural thickening rather than fluid then slurry instillation should proceed according to the TSP.

Patients who have evidence of trapped lung, or who have significant opacification due to fluid on chest x-ray, may have thoracic suction applied if felt appropriate. Another chest x-ray should be considered after a further 18-24 hours of treatment. Patients should undergo slurry instillation once the primary physician is satisfied that at least 50% of the visible pleura are apposed, as judged by visual estimation on chest x-ray. If, by 48 hours post drain insertion, there is inadequate pleural apposition on chest x-ray, or the primary physician feels that talc slurry instillation would be inappropriate for another reason, then further management decisions lie with the primary physician. Such patients should continue to receive follow-up in the standard manner and should have all treatment decisions clearly documented. A flow chart for patient management in the control arm is provided.

Following slurry instillation, patients should be placed on thoracic suction for a minimum of 24 hours, if available and tolerated. Pleural drainage volumes should be recorded at least every 8 hours. Once documented drainage falls below 250mls in the previous 24 hours (in the presence of a patent drain), the drain should be removed, unless the

primary physician feels there is reason for the drain to remain in place for longer (e.g. development of empyema), in which case the reason for delay should be documented.

All patients should have observations carried out as per standard local policy.

Following drain removal, a further chest x-ray should be performed and an appointment given for the first trial follow-up visit at 1 month post randomisation.

4.2.8 Intervention (talc poudrage) arm

Patients should undergo a local anaesthetic thoracoscopy during the procedure list slot allocated for trial intervention. As per normal practice, prior written consent specific for the procedure should be obtained, and a thoracic ultrasound should be performed to confirm a safe volume of fluid is present before proceeding.

All participants who undergo thoracoscopy should have their procedure performed by persons of adequate training and experience. Patients should be given adequate sedation (if required) and local anaesthetic for the procedure. Images should be recorded as per local policy. Biopsy samples should be taken as needed. In those patients at North Bristol and Oxford who consent to trial samples being taken, pleural fluid samples should also be taken, processed and sent as necessary (see section 4.2.9). At the end of the procedure 4g of sterile talc should be sprayed over the pleural surfaces. A 16 – 24 French chest drain should be inserted at the end of the procedure and connected to an underwater seal. Documentation in the patient notes should include the details of the operator(s); the size of the drain inserted; the number of sutures; and the dose and strength of all medications given. Patients should be attached to thoracic suction, if available and tolerated, as soon as is possible post-procedure. This should remain in place for a minimum of 24 hours.

The future care decisions of any patient whose procedure is abandoned or curtailed before poudrage is performed (at the discretion of the operator) remain with the primary physician. Such patients will remain under trial follow-up and should have all care decisions and associated delays clearly documented in their notes.

A chest x-ray (ideally posterior-anterior) should be performed between 18 and 24 hours after drain insertion to assess lung re-expansion. If there is evidence of incomplete re-expansion then drain patency should be checked. Blocked drains should be managed as per local protocol. The management of patients with incomplete lung expansion is at the discretion of the primary physician, and may include the continued use of thoracic suction. The suspected cause of the failure to expand (e.g. trapped lung; persistent air leak; etc.) should be documented in the patient's notes.

For all patients, pleural drainage volumes should be documented at least every 8 hours, with drains remaining in place for a minimum of 24 hours. When a patient has drained 250mls, or less, in the previous 24 hours then the drain should be removed, with appropriate measures taken to ensure wound closure, unless the primary physician feels the drain needs to remain in place for longer (e.g. due to development of empyema,) in which case the reason for delay should be documented. A flow chart for patient management in the intervention arm is provided.

All patients should have observations carried out as per standard local policy.

Following drain removal, a further chest x-ray should be performed and an appointment given for the first trial follow-up visit at 1 month post randomisation.

4.2.9 Visual Assessment Scale (VAS) scoring

All patients should document a VAS score for both thoracic pain and breathlessness during their baseline assessment. This score should then be performed again on the first day post procedure, and then daily for seven days. Following this, scores should be completed on a weekly basis. Patients should attempt to record scores at the same time each day, ideally in the morning.

Following discharge, patients should be provided with the necessary VAS score sheet(s) and given clear, written instructions on how they should be completed. This score sheet should be brought with the patient to each trial visit, or returned to the trial team by post if this is not possible for any reason (e.g. patient death).

If a daily VAS score is missed no attempt at retrospective completion should be made, with this being regarded as missing data. If a weekly VAS score is not completed on the allotted day, although no attempt at retrospective completion should be made, the patient may complete their scores on either of the next two days. After this, scores will be regarded as missing data.

Patients should be made aware that they may be contacted by telephone to remind them to complete VAS scores.

4.2.10 Biological samples and storage

Clinical blood samples

All patients must have blood results available for full blood count, urea and electrolytes, clotting screen, and C-reactive protein from within the ten days preceding their baseline assessment, with results to be entered on the appropriate CRF. Local policies may dictate that other samples, such as a group and hold, be available before any intervention takes place.

On the second day post talc administration, patients should have blood samples sent locally for C-reactive protein, full blood count, and urea and electrolytes, with the results to be entered on the discharge CRF. If a patient is to be discharged before the second day post talc, or has not received talc, these samples should be taken as close to discharge as possible.

Trial samples

At all trial sites, those who consent to trial sample analysis should have 2 EDTA tubes, 1 serum gel tube, and 1 lithium heparin tube of blood taken **('trial blood samples')**. Sites other than Oxford and North Bristol should send these samples as soon as possible, unprocessed, to the Respiratory Research Unit at Southmead Hospital. A matched pleural fluid sample need not be taken in these circumstances.

Patients at North Bristol and Oxford should also have 2 EDTA, 1 serum gel, and 1 lithium heparin tube filled with pleural fluid during either thoracoscopy or initial drain insertion **('trial pleural fluid samples')**. At these sites, trial blood and pleural fluid samples should be centrifuged, labelled and stored locally initially as per the appropriate TSP. All processed samples will eventually be transferred to the Respiratory Research Unit at North Bristol.

All trial-related samples will ultimately be stored in the Respiratory Research Unit / University of Bristol freezer at Southmead Hospital pending cytokine analysis. Genetic compositional analysis may also be undertaken on participants' samples if specific consent for this has been obtained.

4.2.11 Patient diaries

Patients should be provided with pre-printed diaries to keep with them for the duration of their trial involvement. They are to record all personal contact with medical professionals (excluding trial visits) in a basic standardised manner. These data will be reviewed at follow-up appointments and will subsequently be used to determine the health utilisation of each participant during the follow-up period.

Patients should be made aware that they may be contacted by telephone to remind them to complete forms.

4.2.12 Trial follow-up appointments (1, 3 and 6 months)

Trial follow-up appointments will take place at 1 month (day 28+/- 7 days), 3 months (day 84 +/- 10 days), and 6 months (168 days +/- 14 days) post randomisation. If a patient is unable to attend an appointment, and if appropriate, the follow-up CRF may be completed with the patient over the telephone, with the necessary quality of life and VAS scores sent out to them with a pre-paid envelope. Information may also be obtained from patient notes. Appointments which take place outside of these windows, or which are missed, should be reported as a protocol deviation.

These appointments do not replace any standard follow-up appointments which may be arranged as part of routine clinical care, but, for convenience, standard and trial follow-up may be undertaken simultaneously if circumstances allow.

These appointments are to take place in the patient's local trial hospital or appropriate satellite centres. A chest x-ray should be performed and reviewed by a medical member of the trial team, or a radiologist. Patients should undergo a standardised assessment which will include a review of their diary; EQ-5D and SF-36 questionnaires; and a focused medical history.
Patients should ideally be given an appointment for their next follow-up visit before returning home.

4.2.13 Routine follow-up appointments

The frequency of routine follow-up appointments after trial intervention is at the discretion of the primary physician managing the patient's pleural effusion and/or disease. As mentioned above, all effort should be made to co-ordinate trial visits with routine follow-up appointments.

4.2.14 Worsening breathlessness post allocated treatment

Any patient who develops acute breathlessness should contact emergency services in the normal manner. All emergency treatment and investigations are at the discretion of the receiving team. There are to be no restrictions on emergency pleural interventions.

If a patient develops breathlessness more insidiously at any time during their follow-up period, they should contact medical services in a normal manner. This is likely to be via their general practitioner, but arrangements to directly contact their local respiratory department or cancer specialist nurse may have been made previously. In this situation, the primary respiratory physician should be informed, and should determine whether the patient needs to be seen in outpatients' clinic sooner than originally planned. Increasing breathlessness should also be picked up at standard and trial follow-up visits.

4.2.15 Further pleural intervention

All patients who are felt to have increasing breathlessness should undergo a chest x-ray. Any chest x-ray which shows a degree of pleural opacification ipsilateral to the pleurodesis attempt should lead to further imaging to confirm the presence of fluid. If fluid is confirmed, and the chest x-ray shows pleural opacification to be one third or greater than the volume of the hemi-thorax (by visual estimation), the primary physician should undertake any further investigations or interventions as deemed appropriate. In patients who have less than one third of the hemi-thorax occupied by pleural fluid, the primary physician should discuss whether pleural intervention is required with another local physician who is blinded to treatment arm. In the event of disagreement, or being unable to find a blinded physician, the chief investigator should be contacted to make a casting decision (without being informed of the treatment arm).

All decisions regarding pleural interventions, whether undertaken or not, should be clearly documented in the patient's notes.

4.2.16 Thoracic ultrasounds

All ultrasound scans performed in a clinic setting should be performed by operators with sufficient experience and competence. Operators need not be blind to treatment arm, unless providing a second opinion in the case of a small effusion. Scans will be used to assess the presence of fluid and maximum depth in centimetres (standard practice). Where possible, linked-anonymised images should be saved and stored whenever a trial participant undergoes thoracic ultrasound.

4.2.17 Trial images

All trial participants should have their chest x-rays and CTs stored locally during their follow-up period, as per local routine clinical practice. All chest x-ray and CT images

obtained during the patient's follow-up period should be transferred to the study team before the end of trial (EoT) date. Images should be saved in a linked-anonymised form. If it has been possible to securely store ultrasound images during the trial period, these should also be transferred.

4.2.18 End of trial (EoT) date

The trial will cease recruitment on August 31st 2016 (six months before the trial completion date of 31st January 2017 or earlier if either of the following criteria are met:

- The target of 330 patients who are eligible for follow-up has been reached; or
- The Trial Steering Committee (TSC) decides to stop the trial early based on the recommendation from the Independent Data Monitoring Committee (IDMC).

The provisional EoT date will therefore be the last visit of the last patient.

At the end of their 6-month follow-up period patients will be stratified as 'alive' or 'dead,' and survival data collected. Further information regarding participants' mortality may be obtained by accessing the NHS central register. Consent for this information will need to be given separate to trial involvement. This information will not be collected beyond 1 year after the EoT date.

All surviving patients will have their on-going care devolved to the appropriate local services.

SECTION 5 – PATIENT WITHDRAWAL AND FOLLOW-UP COMPLICATIONS

5.1 Patient withdrawal

Patients will have originally consented to trial follow-up, and to sample collection, storage and analysis. Patients have the right to withdraw from the trial at any point. Withdrawal does not have to be justified and will not affect future or on-going care. In the event of withdrawal, any details available for the reason(s) should be recorded in the patient's CRF, and clarification on the nature of the withdrawal of consent, as outlined below, should be sought. Patients may still be stratified as 'alive' or 'dead' at the end of their follow-up period and may still have their mortality data extracted from the NHS central register, unless consent for clinical data use is withdrawn.

5.1.1 Withdrawal of consent to all trial involvement

The patient withdraws all consent for trial involvement, including sample storage and analysis, and for any data already collected to be used in analyses. Samples already taken and follow-up data should be destroyed as per local policy.

5.1.2 Withdrawal of consent to follow-up and further clinical data collection only

The patient withdraws consent to further follow-up visits and recording of clinical data. They maintain consent for blood and fluid samples already taken to be analysed, and for clinical data already collected to be used in analyses.

5.1.3 Withdrawal of consent to follow-up, further clinical data collection, and clinical data use

The patient withdraws consent to further follow-up visits, recording of clinical data, and the use of any clinical data already collected in analyses.
They maintain consent for blood and fluid samples already taken to be analysed.

5.1.4 Withdrawal of consent to sample analysis only

The patient withdraws consent for their previously taken blood and pleural samples to be analysed, or for any data already obtained from such samples to be used in the final analysis. Samples and associated data should be destroyed in line with local policy. They maintain consent for trial follow-up, clinical data collection and the use of this data in the final analysis.

5.1.5 Withdrawal of consent to genetic sample analysis

Patients may withdraw consent for their previously taken blood samples to undergo genetic analysis. This can be done separate to, or in combination with, any of the above withdrawal scenarios.

5.2 Other follow-up complications

If a patient moves to another area outside the trial catchment, every effort should be made to continue follow-up in conjunction with the new local services, or via the new GP. If this is not possible, the patient should be considered as lost to follow up.

SECTION 6 – STATISTICAL CONSIDERATIONS

6.1 Outcome measures

6.1.1 Primary endpoint

The primary endpoint is the number of patients who experience pleurodesis failure up to three months (90 days) post randomisation.
A patient is defined as experiencing pleurodesis failure if they undergo any of the following procedures on the side ipsilateral to their trial intervention:

- Therapeutic pleural aspiration of ≥100mls; or
- Insertion of an intercostal drain for fluid drainage; or
- Insertion of an indwelling pleural catheter; or
- Medical or surgical thoracoscopy.

A patient is also deemed to have failed pleurodesis if their primary physician decides that they require one of the above pleural interventions, but the intervention is not performed (e.g. in the event of death or patient choice against procedure). The primary physician is not blind to treatment arm. Please refer to 4.2.13 for further information on the process of the primary physician deciding upon intervention for breathlessness.

All decisions regarding further pleural interventions in trial participants will be reviewed in a blinded fashion following trial completion using chest x-ray appearances, and if possible ultrasound images, at the time of symptom deterioration.

The overall survival rate from diagnosis of malignant pleural effusion is generally only a few months. For this reason, the primary endpoint will be measured at 3 months as this is likely to be a more clinically relevant period over which pleurodesis failure will impact on patient care and quality of life. The proportion of patients experiencing pleurodesis failure by 1 and 6 months will be secondary outcomes.

6.1.2 Secondary endpoints

1. The number of patients with pleurodesis failure up to 30 days post randomisation.
2. The number of patients with pleurodesis failure up to 180 days post randomisation.
3. Requirement for further pleural procedures up to 180 days post randomisation, based on an independent assessment performed by two adjudicators who are blind to treatment outcome and clinical course.
4. Percentage radiographic (chest x-ray) pleural opacification at the 1-month, 3-month and 6-month post randomisation follow-up visits, and after initial drain removal.
5. Self-reported health-related quality of life at the 1-month, 3-month and 6-month follow-up post-randomisation visits, as measured using the SF-36 and EQ-5D questionnaires.

6. Self-reported thoracic pain and breathlessness at 7 days post procedure, and 30, 90 and 180 days post randomisation, measured using visual-analogue scale (VAS) scores.
7. All-cause mortality up to 180 days post randomisation
8. Time to pleurodesis failure, censored at 180 days post randomisation.
9. Number of nights spent as a hospital inpatient up to 90 days post randomisation, including length of initial stay

6.1.3 Health economic outcomes

Since this trial is being recruited to from within the United Kingdom, the perspective adopted in the economic analysis will be that of the UK National Health Service and Social Services. As a result we will collect information on the following resource use items:

1. *The costs of performing talc pleurodesis using the two interventions under study*. This will entail collecting information on theatre time, staff time, consumables, and subsequent hospitalisation. This information will be obtained by reviewing patients' medical notes. In addition, an average cost per procedure will be estimated by direct observation of a sample of procedures undertaken in each patient group.

2. *Follow-up costs*. This will entail collecting information on patient's use of resources after discharge from hospital. Information collected will include: inpatient stays, outpatient services, use of emergency departments, ambulance costs, use of primary care services and social services. Information on inpatient stays will be obtained by reviewing the administrative care records in each of the participating centres. Other resource use information will be obtained using a patient questionnaire designed to collect information in the trial. This questionnaire will be administered by study staff as part of all the follow-up interviews at 1, 3 and 6 months. To aid patients in their recall process, patients will be supplied at the start of the trial with specially designed patient diaries.

Resource use items will be priced using unit cost schedules such as PSSRU, NHS Trust Financial Returns and NHS Reference costs. If necessary, finance departments at each of the study centres will be contacted to obtain unit cost information not included in these sources.

As the main outcome measure in the economic evaluation will be incremental cost per Quality-Adjusted Life Year (QALY) gained, generic quality of life information will be collected. In line with the recommendations from the National Institute for Health and Clinical Excellence (NICE), the EuroQol EQ-5D – a widely used generic multi-attribute utility scale – will be completed for each patient at baseline and at the 1, 3 and 6 month assessments to measure patients' general health related quality of life. For QALY construction, EQ-5D results will be translated into utility values using published UK population valuations. As a sensitivity analysis, quality of life will also be assessed using the Short-Form 36 (SF-36) – another widely used generic multi-attribute scale. Responses to the SF-36 will be converted into utilities using the SF-6D.

6.2 Sample size

Previous literature and our own audit data suggest that patients with a WHO performance status score of 2 or better have approximate pleurodesis failure rates of 10% with a thoracoscopy, and 30% with standard chest tube and talc slurry pleurodesis [16].

In order to detect a 15% difference in pleurodesis failure at 3 months (10% thoracoscopy and poudrage vs. 25% chest drain and talc slurry) with 90% power, a 5% significance level, and 10% loss to follow-up, we would require 325 patients. This has been rounded up to 330 patients (165 patients in each treatment arm).

6.3 Statistical analysis

The full statistical analysis plan is described in a separate document.

All analyses will be by intention-to-treat (ITT), and will include all randomised patients for whom an outcome is available. Analyses will be two-sided, and will be considered statistically significant at the 5% level. All analyses will adjust for the minimisation factors (type of underlying malignant disease, and WHO/ECOG performance status).

6.3.1 Primary outcome

Pleurodesis failure rates at three months will be analysed using a logistic regression model. Patients who die before three months without having experienced a pleurodesis failure will be classified as pleurodesis successes.

6.3.2 Interim analysis

The Independent Data Monitoring Committee (IDMC) will review trial data at regular intervals to ensure patient safety. There will be no formal interim analyses to assess whether stopping early for efficacy is warranted.

6.3.3 Health economic analysis

An economic evaluation, adherent to guidelines for good economic evaluation practice, will be undertaken integral to the main trial. A within-trial cost-utility analysis will explore the incremental cost per QALY gained of thoracoscopy-delivered talc poudrage when compared to talc slurry pleurodesis. Cost and effect results will be reported as means with standard deviations, with mean differences between the two patient groups reported alongside 95% confidence intervals. Depending on the amount of missing cost and quality of life data, missing data will be imputed using recommended multiple imputation methods, with results from this analysis being presented as an additional sensitivity analysis. Incremental cost-effectiveness will be calculated by dividing the difference in costs by the difference in effects. Uncertainty around the incremental cost-effectiveness ratio (ICER) will be explored using non-parametric bootstrapping.

All cost-effectiveness results will be presented on the cost-effectiveness plane and as cost-effectiveness acceptability curves, indicating where the results fall in relation to a given cost-effectiveness threshold.

Due to the palliative care population involved in the trial and the nature of the intervention, the majority of the benefit and costs will be captured within the 6 month follow-up. Evidence shows that if the intervention is successful at 3 months, there is only a very small proportion of failure after that time point. As a result, we do not envisage that the use of decision modelling will be needed to extrapolate the within trial results.

SECTION 7 – ADVERSE EVENTS

7.1 Definitions

7.1.1 General

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject.

A Serious Adverse Event (SAE) is any untoward and unexpected medical occurrence or effect that:

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgment should be exercised in deciding whether an AE is to be considered serious in other situations.

AEs that are not immediately life-threatening or do not result in death or hospitalization, but which may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should also be considered serious.

7.1.2 Expected AEs

The following are felt to be expected adverse events associated with the routine use of the proposed trial interventions and must be recorded (and reported when appropriate) if they occur. Details of how to record and report events are covered in section 7.2.

1. Anaemia requiring transfusion
2. Post-procedure fever
3. Wound infection
4. Empyema ipsilateral to intervention
5. Bronchopleural fistula
6. Atelectasis requiring bronchoscopy
7. Pneumonia requiring antibiotics
8. Respiratory failure
9. Dysrhythmia
10. Myocardial infarction
11. Deep vein thrombosis
12. Pulmonary embolus
13. Surgical emphysema
14. Drain dislodgement or replacement

7.2 Recording and reporting procedures

Any questions concerning adverse event reporting should be directed to the Trial coordinator, trial manager or Chief Investigator in the first instance.

The population involved in this study is likely to have a significant number of co-morbidities. As such, many serious adverse events unrelated to trial interventions, including death or hospital admission due to malignant disease progression, are to be anticipated during the period of trial follow-up. With this in mind, reporting procedures relating to serious adverse events will differ depending on the nature of the event and when the event occurs.

The following two sections describe recording and reporting procedures for AEs and SAEs. The term “discharge” refers to the end of the inpatient stay relating to the allocated trial intervention.

7.2.1 Events occurring prior to discharge

All AEs which occur during trial participants’ initial hospitalisation, including those expected events listed in section 7.1.1, should be recorded on the discharge CRF and on an AE form. A separate AE form should be completed for each event. Should any of these events meet the criteria for an SAE, it should also be recorded on an SAE form and reported to the trial teams at the ORTU and North Bristol, and the Sponsor. Reporting of SAEs should occur within 24 hours of the local trial team becoming aware of the event.

7.2.2 Events occurring following discharge

All AEs which occur once a patient has been discharged following their initial hospitalization, including those listed in section 7.1.1, should be recorded on the next follow-up CRF with a separate AE form completed for each event as previously described.

Any event occurring following discharge which meets the criteria for an SAE should be discussed with the local principal investigator. If, in their opinion, there is a reasonable possibility that the event is related to the trial intervention, or if the event is of particular medical interest, it should be recorded on an SAE form and reported to the trial manager (ORTU, Oxford), trial coordinator (North Bristol) and the Sponsor (North Bristol). Reporting of SAEs should occur within 24 hours of the local trial team becoming aware of the event.

Other events which meet the criteria for an SAE, but which are not felt by the PI to be of relevance to the trial (such as, for example death or admission due to disease progression), need not be reported.

7.3 Following reporting

All reported events should be followed to resolution, including those which lead to withdrawal from the trial. The decision to withdraw a patient from the trial due to an

adverse event or reaction rests with the principal investigator. Should a patient request withdrawal, outcome data will still be gathered unless consent for this is also withdrawn.

SECTION 8 – TRIAL INFRASTRUCTURE

8.1 Trial Management Group (TMG)

The TMG is responsible for the day-to-day management of the trial. The team is responsible for all aspects of the project (such as recruitment rate, budget management, protocol adherence, etc.) and for ensuring appropriate action is taken to safeguard trial participants and the quality of the study.

The TMG consists of:

- Dr Nick Maskell, Chief Investigator (CI) and principal investigator for Bristol.
- Dr Rahul Bhatnagar, Trial Co-ordinator (TC) and a Clinical Research Fellow based at Southmead Hospital in Bristol
- Dr Najib Rahman, Oxford Respiratory Trials Unit (ORTU) Clinical director, Key investigator and principal investigator for Oxford.
- Miss Hania Piotrowska, Trial Manager.
- Mrs Natalie Zahan-Evans, Lead Trial Nurse
- Mr Brennan Kahan, Trial Statistician

8.2 Trial Steering Committee (TSC)

The TSC consists of both independent members as well as researchers working on the trial. The role of the TSC is to provide overall supervision of the study and monitor the progress of the trial to ensure that it is being conducted in accordance with the protocol, relevant regulations and the principles of GCP. The TSC will meet at regular intervals and will comprise:

Independent Chairperson	Professor Robert Miller
Chief Investigator	Dr Nick Maskell
Trial Statistician	Mr Brennan Kahan
Independent Member	Dr John Harvey
Independent Member	Dr Clare Hooper
Independent Member	Dr Helen Davies
Patient Representative	Mrs Merle Sivier
Patient Representative:	Mrs Julie Naas

8.3 Independent Data Monitoring Committee (IDMC)

The IDMC is independent of the trial investigators. Its role is to review study safety data and provide advice to the TSC as to whether recruitment can continue.

Independent statistician	Ms Ly-Mee Yu
Independent physician	Professor Tim Peto
Independent physician	Professor Duncan Geddes

8.4 Recruiting centres and principal investigators

Southmead Hospital, North Bristol	Dr Nick Maskell
Churchill Hospital, Oxford	Dr Najib Rahman
Nottingham City Hospital, Nottingham	Dr Wei Shen Lim
Medway Maritime Hospital, Kent	Dr Gihan Hettiarachchi
King's Mill Hospital, Sutton-in-Ashfield	Dr Mark Roberts
Addenbrooke's Hospital, Cambridge	Dr Pasupathy Sivasothy
Musgrove Park Hospital, Taunton	Dr Justin Pepperell
Royal Preston Hospital, Preston	Dr Mohammed Munavvar
Wythenshawe Hospital, Manchester	Dr Mohamed Al-Aloul
St. Thomas' Hospital, London	Dr Alex West
Doncaster Royal Infirmary, Doncaster	Dr Moe Kyi
University Hospital of North Tees, Stockton-on-Tees	Dr Richard Harrison
Aintree Hospital, Liverpool	Dr Biswajit Chakrabarti
Southern General Hospital, Glasgow	Dr Kevin Blyth
Queen Elizabeth Hospital, Birmingham	Dr Benjamin Sutton
Milton Keynes Hospital, Milton Keynes	Dr Aji Kavidasan

SECTION 9 – ETHICAL ISSUES

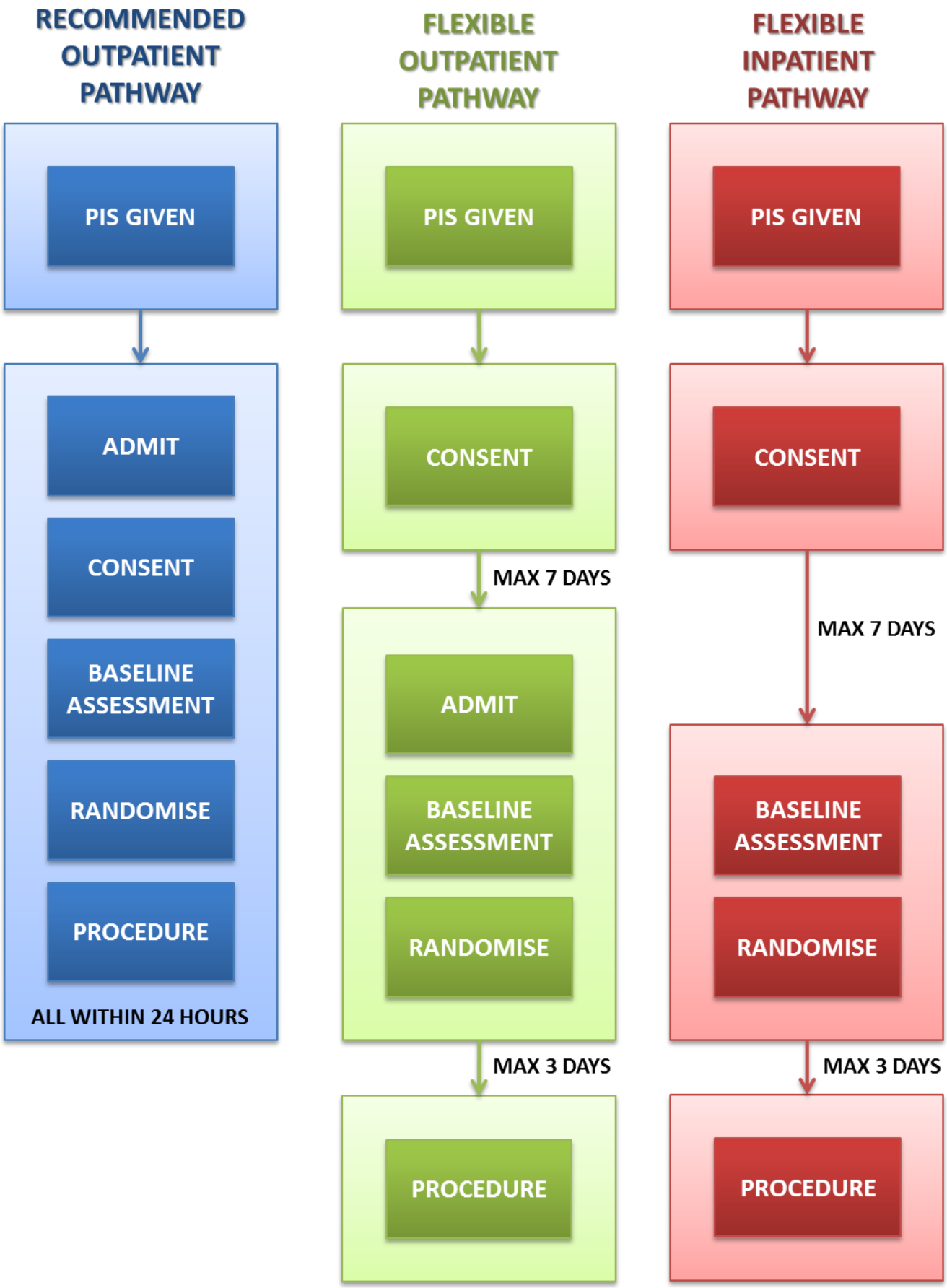
There are currently no robust data on which to base the decision of whether talc poudrage or slurry should be used to maximise pleurodesis efficacy, and therefore use of NHS resources, and minimise potential complications. Current decisions on pleurodesis method are thus based on weak evidence and provision of services locally. Current clinical practice does not, therefore, provide a rational choice to patients on the basis of evidence, and both patient time and NHS resources are potentially wasted using a less than optimal treatment strategy.

Approval from the relevant ethical bodies will be obtained before trial recruitment commences. All participants in the study will have a clinical requirement for a pleurodesis procedure on the basis of current national guidelines and the inclusion criteria, and thus their participation in the study does not pose risks to them solely as a result of study participation. All centres involved in trial recruitment are experienced in both methods of talc pleurodesis and therefore there are no additional risks of a novel technique.

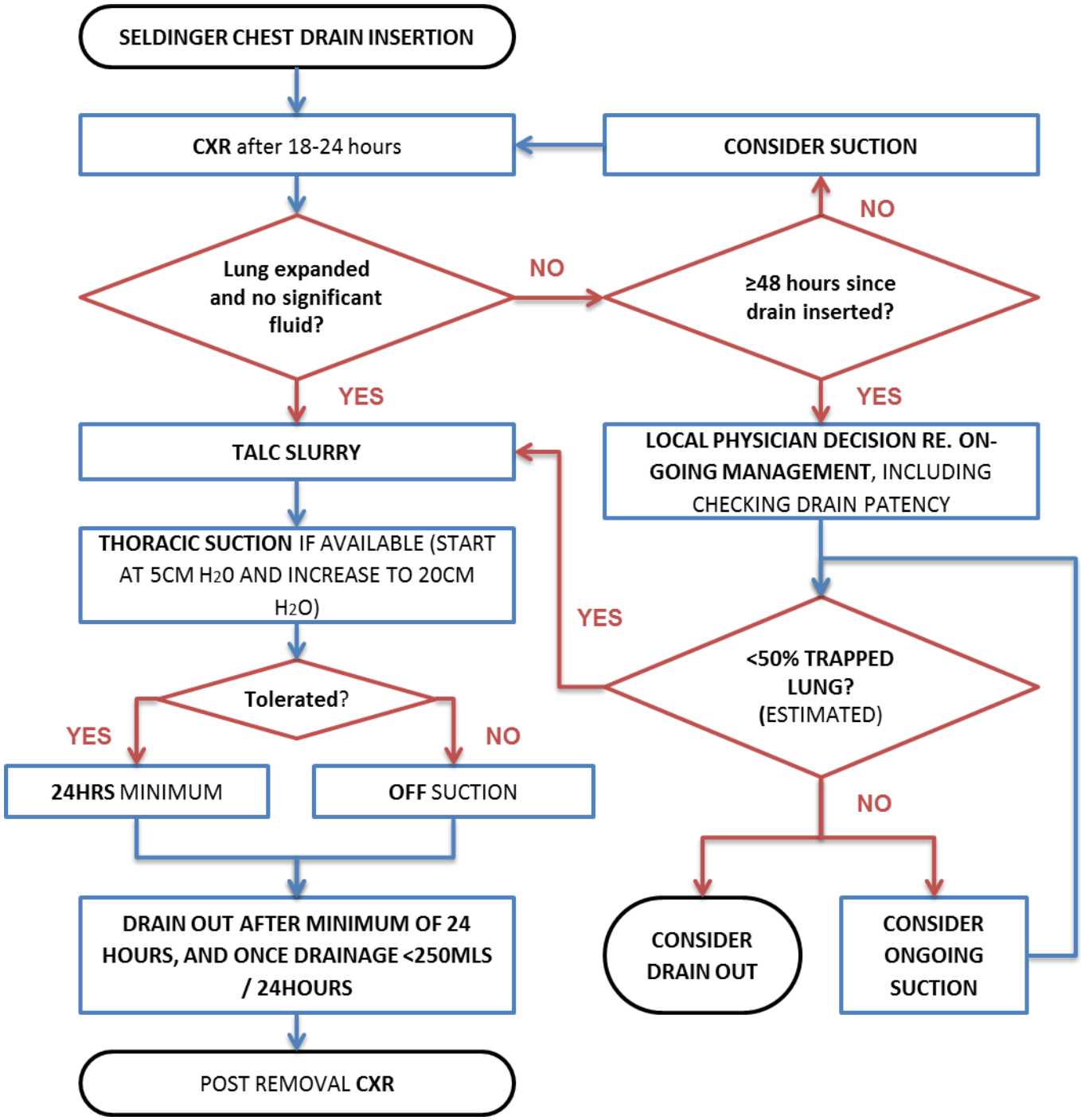
Consent for the any trial intervention will occur to GMC standards, including a discussion of potential risks and alternative treatment strategies in every case. Written, informed consent for participation in the study will be obtained in every case, with adequate reflection time provided, and included information on risks and benefits of each procedure and the rationale for the study. Participants will be closely followed for pleurodesis failure, and treated for symptomatic failure at the first opportunity as part of the study protocol. Fully anonymised trial documentation will be securely preserved for at least 5 years after study completion and thereafter disposed of according to regulatory requirements.

There is no evidence that talc increases either morbidity or mortality in patients with malignant pleural effusions. Talc, as used in the context proposed in this trial, is not regarded as a new Investigational Medicinal Product (IMP). No other new IMPs are to be used in the trial.

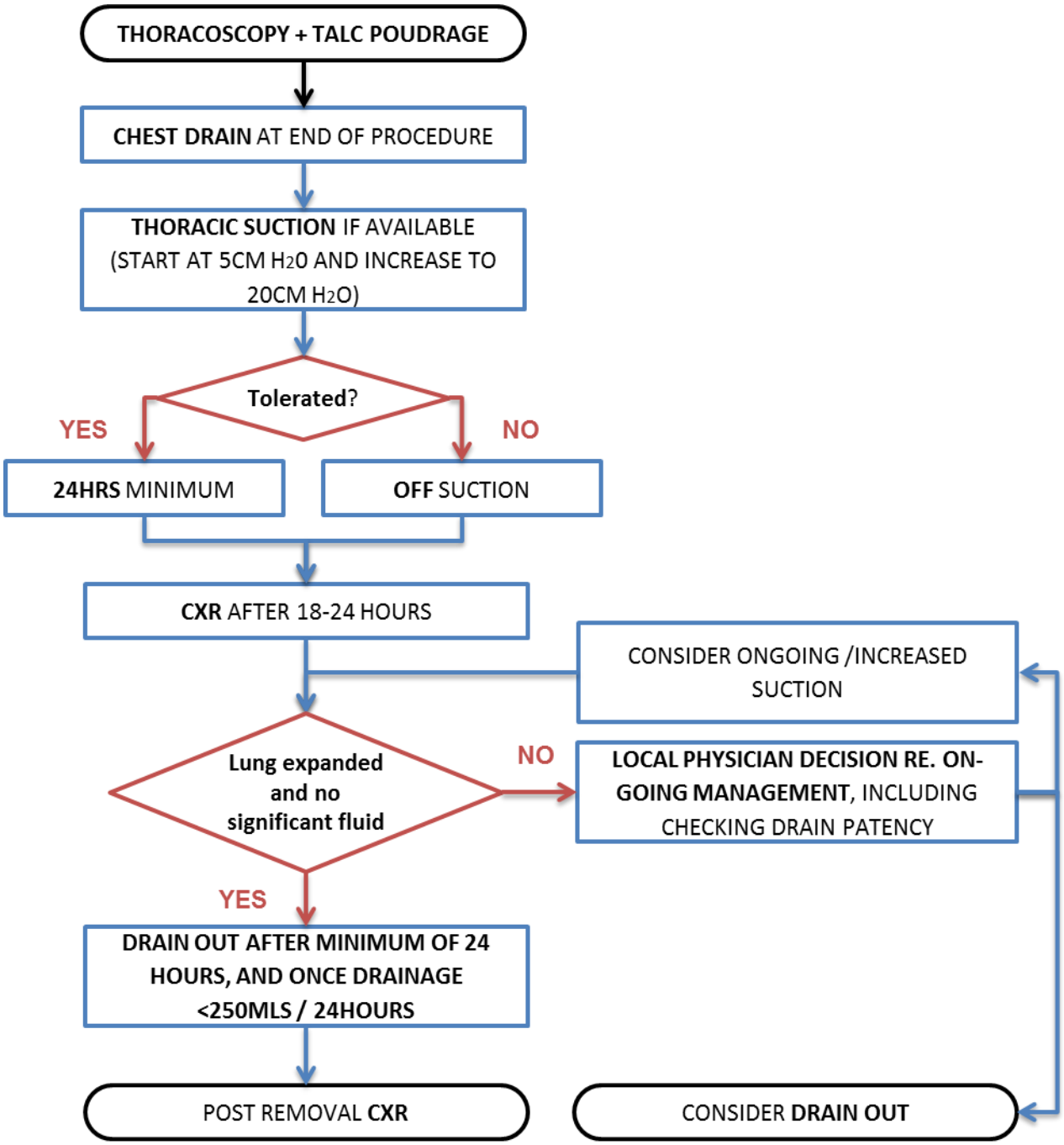
APPENDIX 1 – ADMISSION SUMMARY FLOW CHARTS



APPENDIX 2 – FLOW CHART FOR PATIENTS IN SLURRY ARM



APPENDIX 3 – FLOW CHART FOR PATIENTS IN POUDRAGE ARM



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APPENDIX 5 – ABBREVIATIONS

AE	Adverse Event
BTS	British Thoracic Society
CI	Chief Investigator
CRF	Case Report Form
CT	Computed Tomography
CXR	Chest X-Ray
ECOG	Eastern Co-operative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EoT	End of Trial
EQ-5D	EuroQol-5D
F	French
g	Grams
GCP	Good Clinical Practice
GMC	General Medical Council
Hrs	Hours
HTA	Health Technology Assessment
ICER	Incremental Cost-Effectiveness Ratio
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
IPC	Indwelling Pleural Catheter
ISRCTN	International Standard Randomised Controlled Trial Number
ITT	Intention to Treat
LAT	Local Anaesthetic Thoracoscopy
MDT	Multidisciplinary Team
ml or **mls**	Millilitres
MPE	Malignant Pleural Effusion
MRI	Magnetic Resonance Imaging
NHS	National Health Service
NICE	National Institute for Clinical Excellence
ORTU	Oxford Respiratory Trials Unit
PA	Posterior-Anterior
PSSRU	Personal Social Services Research Unit
QALY	Quality-Adjusted Life Year
QoL	Quality of Life
R&I	Research and Innovation
REC	Research Ethics Committee
SAE	Serious Adverse Event
SF-36	Short Form 36
SOB	Shortness of Breath
TC	Trial Coordinator
TMG	Trial Management Group
TSC	Trial Steering Committee
TSP	Trial Specific Procedure
UK	United Kingdom
USA	United States of America
VAS	Visual Assessment Scale
WHO	World Health Organisation

APPENDIX 6 – PROTOCOL AMENDMENT HISTORY

Amendment number	Details of significant alterations to protocol	Resulting protocol version and date
1	• Clarified various sections in the protocol • Altered the time window for a patient to consider trial entry • Updated flow charts • Clarified the use of suction and telephone follow ups.	**2.0 01/12/2012**
2		
3	• Adjustments to the follow up visit windows • Administrative details were updated throughout the protocol.	**3.0 14/08/2013**
4	• Change of time allowance between the randomisation and the study procedure from 24 to 72 hours • Minor admin changes and clarifications to the protocol.	**4.0 26/09/2013**
5		
6	• Edited the safety reporting section of the protocol • Updated administrative details throughout the protocol • Added appendix 6	**5.0 01/06/2014**
7	• Updated secondary endpoints following ratification of statistical analysis plan version 1.0 • Updated study end date • Updated trial recruitment centre and PI details • Minor clarifications	**6.0 06/10/2014**
8	• Clarified that the first 7 days of VAS measurements are to be taken post procedure, not post randomization • Removed Leicester as recruiting site	**7.0 05/12/2014**