

BMJ Open Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial

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ABSTRACT

Introduction: The management of recurrent malignant pleural effusions (MPE) can be challenging. Various options are available, with the most efficacious and widely used being talc pleurodesis. Talc can either be applied via a chest drain in the form of slurry, or at medical thoracoscopy using poudrage. Current evidence regarding which method is most effective is conflicting and often methodologically flawed. The TAPPS trial is a suitably powered, multicentre, open-label, randomised controlled trial designed to compare the pleurodesis success rate of medical thoracoscopy and talc poudrage with chest drain insertion and talc slurry.

Methods and analysis: 330 patients with a confirmed MPE requiring intervention will be recruited from UK hospitals. Patients will be randomised (1:1) to undergo either small bore (<14 Fr) Seldinger chest drain insertion followed by instillation of sterile talc (4 g), or to undergo medical thoracoscopy and simultaneous poudrage (4 g). The allocated procedure will be performed as an inpatient within 3 days of randomisation taking place. Following discharge, patients will be followed up at regular intervals for 6 months. The primary outcome measure is pleurodesis failure rates at 3 months. Pleurodesis failure is defined as the need for further pleural intervention for fluid management on the side of the trial intervention.

Ethics and dissemination: The trial has received ethical approval from the National Research Ethics Service Committee North West—Preston (12/NW/0467). There is a trial steering committee which includes independent members and a patient and public representative. The trial results will be published in a peer-reviewed journal and presented at international conferences, as well as being disseminated via local and national charities and patient groups. All participants who wish to know the study results will also be contacted directly on their publication.

Trial registration number: ISRCTN47845793.

Strengths and limitations of this study

- Suitably powered multicentre, randomised controlled trial of talc pleurodesis interventions in the general malignant pleural effusion population.
- First study to specifically investigate poudrage using medical thoracoscopy.
- Robust 6-month patient follow-up.
- Clinically relevant and applicable definition of pleurodesis success.
- Pleurodesis performed as part of diagnostic thoracoscopy not included.
- No comparison with indwelling pleural catheters.

INTRODUCTION

Pleural effusions are a common complication of many cancers, with symptoms often requiring intervention. Data from 10 years ago suggest that there are up to 175 000 new cases of malignant pleural effusion (MPE) in the USA per year and around 40 000 cases per year in the UK,¹ 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.

Pleurodesis is the adherence of the visceral and parietal pleura, which causes an obliteration of the pleural space. Removing the pleural space reduces the possibility of pleural fluid build-up, which means that induction of pleurodesis is considered the mainstay of treatment for recurrent MPE. Many substances have been shown to induce chemical pleurodesis, although by far the most commonly used one in Europe and North America is talc, which has been shown to be superior to alternatives such as tetracycline or bleomycin.² Overall, pleurodesis success rates with talc are typically high,

ranging from 81% to 100%,³ 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 to hospital for chest tube insertion and fluid drainage. Talc is administered as slurry and is made up with a physiologically inert fluid such as 0.9% saline. The chest tube is removed once subsequent drainage volumes become low, potentially indicating successful pleurodesis.

An alternative to this approach is the application of sterile talc powder under direct vision at thoracoscopy (insufflation or poudrage). However, despite an increasing number of hospitals having access to medical thoracoscopy, it is still much less ubiquitous than Seldinger chest 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. 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 limiting reliability. A number of studies regarding talc slurry and talc poudrage were compared as part 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.² 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. Post hoc subgroup analysis demonstrated a rise in pleurodesis success once patients with trapped lung were excluded, as well as a significant difference between poudrage (82%) and slurry (71%; $p=0.045$).⁴

The role of talc poudrage for the induction of pleurodesis and the prevention of fluid recurrence in MPE 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.

METHODS AND ANALYSIS

This study, evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial), is a multicentre, open-label, randomised controlled trial. The trial is sponsored by the North Bristol NHS Trust (NBT) and coordinated jointly by the Academic Respiratory Unit at the University of Bristol and the Oxford Respiratory Trials Unit (ORTU) at the University of Oxford. Data management is undertaken

by the ORTU. The trial is registered on the International Standardised Randomised Controlled Trial Registry (ISRCTN47845793) and funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme. The study is included in the NIHR Clinical Research Network portfolio (ID: 12537). The trial will be conducted in accordance with the Declaration of Helsinki and good clinical practice (GCP).

The primary research question is: For patients with a confirmed MPE and good performance status, does thoracoscopy and talc poudrage increase the proportion of patients with successful pleurodesis at 3 months post-procedure, when compared with standard therapy with chest drain insertion and talc slurry instillation?

The secondary research questions are:

1. Does talc poudrage reduce the time to pleurodesis failure at 3-month and 6-month postprocedure when compared with talc slurry?
2. Does talc poudrage at thoracoscopy improve chest X-ray (CXR) appearances after initial drain removal, and at 1-month, 3-month and 6-month postrandomisation when compared with talc slurry?
3. Does talc poudrage cause less breathlessness and thoracic pain for the first 7 days postrandomisation when compared with talc slurry?
4. Does talc poudrage improve health-related quality of life over the 6 months of postrandomisation when compared with talc slurry?
5. Is talc poudrage cost-effective over 6 months when compared with talc slurry instillation?
6. Does talc poudrage reduce healthcare utilisation during the 6-month postrandomisation when compared with talc slurry instillation?

Setting

Three hundred and thirty patients requiring a pleurodesis intervention for a confirmed MPE will be recruited from UK hospitals (see online supplementary appendix 1 for details of recruiting centres). Patients will be randomised to undergo either chest drain insertion followed by 4 g talc slurry instillation, or to undergo medical thoracoscopy with 4 g talc poudrage. The study flow diagram is shown in figure 1.

Subject screening and selection

Patients with MPE will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT), at routine outpatient appointments and during inpatient reviews. Eligible patients will be invited to participate on a consecutive basis, and will be provided with a patient information leaflet at the earliest opportunity (see online supplementary appendix 2). Patients can be enrolled only once into the TAPPS trial.

Inclusion criteria

1. Clinically confident diagnosis of MPE requiring pleurodesis, defined as:

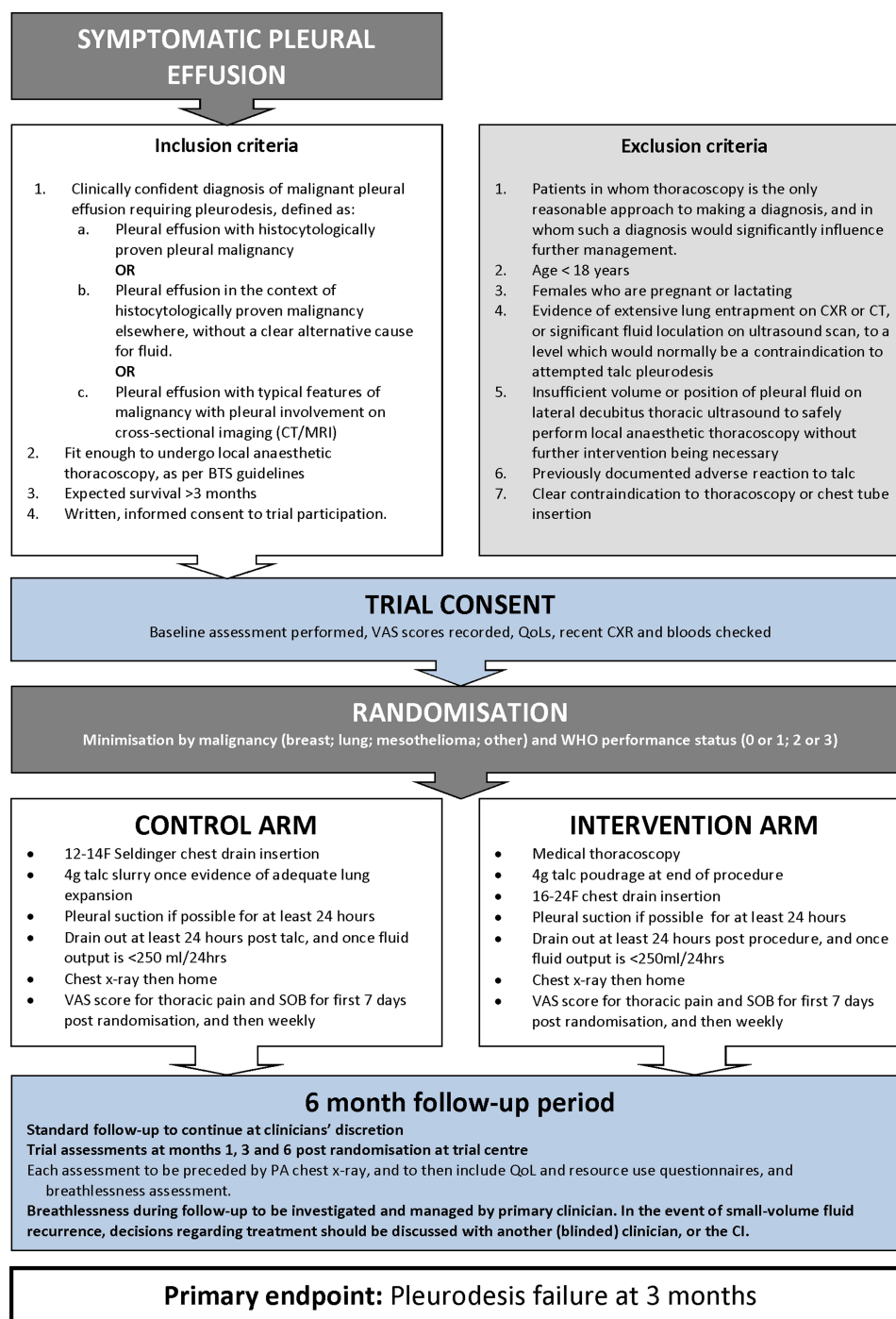


Figure 1 Trial flow chart (BTS, British Thoracic Society; CI, chief investigator; CXR, chest X-ray; QoL, quality of life; VAS, visual assessment scale; PA, pleural apposition; SOB, shortness of breath).

- 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 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.
- 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 a CT scan, or significant fluid loculation on an 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.

Informed consent

A doctor will confirm patient eligibility prior to consent being taken. Participation in the trial will be discussed with the patient by a medical or nursing member of the local trial team. Patients will be given sufficient time (in their own opinion) to fully consider trial entry, as well as to ask questions of investigators. The consent form (see online supplementary appendix 3) will be countersigned by either a medical or nursing member of the trial team.

Randomisation

Following informed consent, 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. Although the allocated trial procedure may be performed within 3 days of randomisation, every effort should be made to perform the procedure immediately afterwards.

Treatment allocation will be performed over the telephone by the ORTU. The randomisation sequence will be generated using a validated, online randomisation service (Sealed Envelope, London, UK; <http://www.sealedenvelope.com>).

The minimisation factors are:

- ▶ Type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other);
- ▶ WHO/Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1; 2 or 3).

Patients and clinicians will not be blinded to treatment allocation.

Standard care

All patients should have been discussed in their local or regional tumour-specific MDT. For all issues other than those pertaining to the drainage and management of the MPE, treatment discretion lies with the primary clinician.

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.

Patients can withdraw from the trial at any time without their clinical care being affected.

Co-enrolment in other clinical trials will be discussed on an individual patient basis, but patients should not be co-enrolled into any trial which specifically aims to directly influence pleural fluid production or drainage.

Interventions

The full trial specific procedures (TSP) for the two treatment arms can be found in online supplementary appendices 4 and 6.

Control (talc slurry) arm

Patients will have a small-bore (<14 Fr) chest drain inserted under aseptic conditions using the Seldinger technique, with appropriate local anaesthesia and premedication as necessary. A suitable site for drain placement will be identified using contemporaneous ultrasound. Drains will only be inserted by persons with adequate training and experience. Trial pleural fluid samples (see section below) should also be taken as necessary.

A CXR should be performed between 18 and 24 h after drain insertion. If there is no evidence of trapped lung or significant fluid, as determined by the patient's primary physician, then the patient should have 4 g 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 CXR, may have thoracic suction applied if it is felt appropriate. Patients should undergo slurry instillation once the primary physician is satisfied that at least 50% of the visible pleura are apposed. If, by 48 h post drain insertion, there is inadequate pleural apposition on CXR, 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 (see online supplementary appendix 5).

Following slurry instillation, thoracic suction should be applied if available and tolerated. Once documented drainage falls below 250 mL per 24 h (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. Following drain removal, a further CXR should be performed and an appointment given for the first trial follow-up visit at 1-month postrandomisation.

Intervention (talc poudrage) arm

All participants who undergo thoracoscopy will have their procedure performed by persons with adequate training and experience. Patients will be given adequate sedation (if required) and local anaesthetic for the procedure. Biopsy samples will be taken as needed. Trial pleural fluid samples (see section below) should also be taken as necessary. At the end of the procedure, 4 g of sterile talc should be sprayed over the pleural surfaces. A 16–24 Fr chest drain should be inserted at the end of the procedure and connected to an underwater seal. Patients should be attached to thoracic suction, if available and tolerated.

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 CXR should be performed between 18 and 24 h after drain insertion to assess lung re-expansion. If there is evidence of incomplete re-expansion, then drain patency should be checked. 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.

All patients' drains should remain in place for a minimum of 24 h. When a patient has drained 250 mL or less in the previous 24 h, then the drain should be removed, unless the primary physician feels that it needs to remain in place for longer. A flow chart for patient management in the intervention arm is provided (see online supplementary appendix 7). Following drain removal, a further CXR should be performed and an appointment given for the first trial follow-up visit at 1-month postrandomisation.

Data collection and management

Visual assessment scale (VAS) scoring

All patients will document a VAS score for thoracic pain and breathlessness during their baseline assessment. This score should then be performed again on the first day postrandomisation, and then daily for 7 days. Following this, scores should be completed on a weekly basis.

Patient diaries

Patients will be provided with preprinted diaries. 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.

Biological samples and storage

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. 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. Genetic compositional analysis may also be undertaken on participants' samples if specific consent for this has been obtained.

Additionally, on the second day post talc administration (or on discharge if sooner), patients should have blood samples taken and analysed locally for C reactive protein, full blood count, and urea and electrolytes, with the results entered onto the discharge case report form.

Trial follow-up appointments

Trial follow-up appointments will take place at 1-month, 3-month and 6 month postrandomisation, with telephone follow-ups being performed if necessary. A CXR will be performed and patients will undergo a standardised assessment, including a review of their healthcare resource use diary; EQ-5D and SF-36 quality of life questionnaires; and a focused medical history.

Further pleural intervention

All patients who are felt to have increasing breathlessness should undergo a CXR. Any CXR 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 CXR shows pleural opacification to be one-third or greater than the volume of the hemithorax (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 hemithorax occupied by pleural fluid, the primary physician should discuss with another local physician who is blinded to the treatment arm whether pleural intervention is required.

Data management

Clinical Record Forms (CRF) will be completed by the trial team at recruiting centres and sent to the ORTU. Data will then be entered onto the trial database (OpenClinica clinical trials software). Missing data and data queries will be highlighted to the trial teams on a monthly basis. The CRFs will only identify patients using their personal trial identification number (no identifiable patient information).

Primary outcome

The primary outcome is the number of patients who experience pleurodesis failure up to 3 months (90 days) postrandomisation.

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 ≥ 100 mL; 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. The primary physician is not blind to the treatment arm; however, all decisions to intervene or not in effusions which occupy less than or equal to one-third of the hemithorax will be discussed with a second clinician who is blind to treatment allocation.

Secondary outcomes

The trial's secondary outcomes are:

1. The number of patients with pleurodesis failure up to 30 days postrandomisation.
2. The number of patients with pleurodesis failure up to 180 days postrandomisation.
3. Requirement for further pleural procedures up to 180 days postrandomisation, based on an independent assessment performed by two adjudicators who are blind to the treatment outcome and clinical course.
4. Percentage pleural opacification (on CXR) at 1-month, 3-month and 6-month postrandomisation follow-up visits, and after initial drain removal.
5. Self-reported health-related quality of life at 1-month, 3-month and 6-month follow-up postrandomisation visits, measured using SF-36 and EQ-5D questionnaires.
6. Self-reported thoracic pain and breathlessness (postrandomisation) at 7, 30, 90 and 180 days, measured using VAS scores.
7. All-cause mortality up to 180 days postrandomisation.
8. Time to pleurodesis failure, censored at 180 days postrandomisation.
9. Number of nights spent in the hospital up to 90 days postrandomisation, including length of initial hospital stay.

Sample size calculation

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 $\leq 10\%$ with thoracoscopy, and $\geq 30\%$ with a 'best standard of care' standard chest tube and talc slurry pleurodesis.⁵

In order to detect a $\geq 15\%$ 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, the study requires 325 patients. For the present analysis, numbers have been rounded up to include 330 patients (165 patients in each treatment arm).

Statistical analysis plan

The full statistical analysis plan is published elsewhere.

The primary analysis for each outcome will be by intention to treat. All tests will be two-sided, and will be considered statistically significant at the 5% level. For each analysis, the following summaries will be provided:

- ▶ The number of patients in each treatment group who are included in the analysis.
- ▶ The mean (SD) or median (IQR) in each treatment group for continuous outcomes, or the number (%) of patients experiencing an event for binary or time-to-event outcomes (time-to-event outcomes will also present the median time to event in each treatment arm if applicable).
- ▶ The treatment effect (difference in means for continuous outcomes, OR for binary outcomes, HR for time-to-event outcomes, rate ratio for count outcomes) with its 95% CI and a p value.

All analyses will adjust for minimisation variables (type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other) and WHO performance status (0–1 or 2–3)).^{6–9} The minimisation variables will be included as covariates in the regression model for each outcome.

CONSORT data will be presented, including: the number of patients screened for the study; the numbers randomised; the numbers receiving the interventions; the numbers lost to follow-up and excluded (with reasons) and the number of patients included in the primary analysis.

Subgroup analyses will be performed for the primary outcome, and the following secondary outcomes: pleurodesis failure at 30 and 180 days; requirement for further pleural procedures; and percentage CXR opacification. Results from subgroup analyses will be viewed as hypothesis generating, and will not be used to make definitive statements about treatment efficacy in a specific subgroup of patients. The following subgroup analyses will be performed:

- ▶ Patients receiving anticancer therapy at baseline versus those not receiving;
- ▶ Previous radiotherapy to chest versus no previous radiotherapy to chest;
- ▶ WHO performance status 0–1 versus 2–3;
- ▶ Patients on non-steroidal anti-inflammatory drugs (NSAIDs) at baseline versus those not on NSAIDs at baseline;
- ▶ Patients on steroids at baseline versus those not on steroids at baseline;
- ▶ Previous attempt at pleurodesis within the past month versus no attempt in the past month;
- ▶ Patients with primary malignancy of breast cancer versus mesothelioma versus lung cancer versus other.

Changes to the protocol after trial commencement

The trial details documented here are consistent with the TAPPS Trial protocol V.6 (date: 06/10/2014).

A summary of the trial amendments can be found in online supplementary appendix 8.

In September 2013, the 'window' in which individuals could undergo their allocated trial procedure was extended from 24 to 72 h postrandomisation.

End of trial

The trial will end once 330 patients have been recruited and all patients have died or completed 6 months of trial follow-up (whichever is sooner).

ETHICS AND DISSEMINATION

Monitoring

An independent data monitoring committee (IDMC) will be convened at regular intervals, consisting of members who are independent of the trial investigators. The role of the IDMC is to review study safety data and provide advice to the trial steering committee (TSC), specifically as to whether recruitment can continue. No interim analysis is planned.

Safety reporting

Data will be collected at each patient's trial visit regarding any serious adverse events (SAE; as defined by GCP). All SAEs causally related to trial interventions will be reported to the sponsor and to the relevant oversight bodies, and will be followed until they resolve or stabilise.

Trial monitoring and oversight

The TSC will be responsible for overseeing the progress of the trial and will meet at approximate six monthly intervals. The TSC will comprise of independent chairperson, independent members, statistician, patient and public representative and members of the trial team.

Dissemination

The trial will be publicised at regional and national conferences. The final results will be presented at scientific meetings and published in a peer-reviewed journal (authorship will be according to the journal's guidelines). In addition, a lay summary of the study results will be circulated to potentially interested parties.

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Contributors NAM and NMR conceived the initial trial concept. All authors contributed to the development of the trial design and protocol. NMR and BCK carried out the sample size calculations. RB, BCK, NMR, RFM and NAM wrote the statistical analysis plan. All authors have read and approved this manuscript.

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Competing interests None.

Ethics approval The trial and all substantial amendments have been reviewed and granted approval by the National Research Ethics Service (NRES) Committee North West—Preston (12/NW/0467).

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

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APPENDIX 1 – TAPPS RECRUITING CENTRES AND PRINCIPAL INVESTIGATORS

Southmead Hospital, North Bristol	Dr Nick Maskell (Chief Investigator)
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
Bristol Royal Infirmary, Bristol	Dr Roland Jenkins
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
Glenfield Hospital, Leicester	Dr Neil Martin
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

PATIENT INFORMATION SHEET

TAPPS TRIAL

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.

1. Invitation

You are being invited to take part in a research study called the TAPPS trial. Before you decide whether or not to be involved, it is important for you to understand why we are conducting this study and what it will mean for you. Please feel free to discuss this information with someone else, such as your family or GP, if you wish. Please ask any questions if you feel there is something which is not clear, or if you would like to know more.

2. Trial description

This is a research study which aims to help determine the best way to manage fluid collections around the lungs (pleural effusion) which are caused by cancer (malignancy). It will look to compare two treatment methods which both involve the application of sterile talc powder to the lining of the lung. This aims to 'stick' the lung to the chest wall and so prevent further fluid build-up.

One group of patients will receive a small chest tube to drain away the fluid, before having sterile talc powder (mixed with water to form slurry) inserted through the same tube. The other group of patients will undergo a minor procedure called a thoracoscopy. This involves using a small camera to inspect the lining of the lung and allows the talc to be sprayed evenly over its surface. The main aim of this trial is to see which method is the most effective at preventing the fluid building up again.

This is a 'randomised trial,' which means that you will be randomly allocated to receive one or the other of the treatments described above. We shall not be able to influence or predict which treatment you receive.

3. What is the purpose of the trial?

Patients with cancer can develop fluid around the lungs as part of their disease process. This fluid is called a malignant pleural effusion. The pleura are thin layers which normally cover the lungs and help them to move against the chest wall. Fluid which builds up between these layers can restrict lung movement, causing breathlessness, but can usually be drained away

to help relieve symptoms. However, fluid caused by cancer will often come back after drainage, sometimes within a few days. To reduce the chances of this happening, doctors can apply an irritant substance to the pleura to try to cause them to stick together, and so prevent any further fluid from building up. This process is called pleurodesis, with the most widely used irritant being sterile talc.

Talc is most commonly given in slurry form, in which a fine powder is mixed with water without it dissolving. Before this can be given, the effusion needs to be drained away using a small chest tube (placed under local anaesthetic) which is then also used to administer the slurry. This method is established and proven, and usually involves a hospital stay of around five to seven days before the drain can be taken out.

An alternative to this involves performing a minor procedure called a thoracoscopy. This technique is also done under local anaesthetic, but often requires a small amount of light sedation as well. During a thoracoscopy, a small camera is inserted through the chest wall and any pleural fluid is drained away before talc powder is sprayed directly onto the pleura, a process known as poudrage. A chest tube is left in place afterwards to allow the lung to re-expand, and can normally be removed after one to two days. Patients who undergo thoracoscopy are normally in hospital for two to three days in total.

There have been previous studies which have attempted to identify which of these two methods is the best way to apply talc, but none so far have been able to provide doctors and patients with a complete answer. This study therefore looks to definitively establish which method of applying talc, slurry or poudrage, is the most effective at preventing fluid recurrence for patients, and the most cost-effective for healthcare providers such as the NHS. We shall also be collecting information on patients' symptoms and quality of life during the trial to see if one treatment is better than the other from the patient point of view.

4. Why have I been chosen?

We have invited you to take part in this trial because you have a pleural effusion caused by your cancer. You are also considered well enough to undergo either a thoracoscopy under local anaesthetic, or a standard chest drain insertion, and to receive sterile talc. The results of this trial will help to inform the future management of patients in your situation.

This study will take place in hospitals in different parts of the country. We are going to ask 330 patients in total to participate.

5. Do I have to take part?

No, it is up to you alone to decide whether you take part. If you do decide to participate then you will be asked to sign a consent form. You will be given a copy of the consent form and this information sheet for your records.

If you decide to take part but later change your mind you are free to withdraw at any time, without giving a reason. A decision to not take part, or to withdraw, will not affect your rights or your future medical care outside of the trial.

6. If I agree to participate, will I definitely have one of the procedures, and will I definitely receive talc?

Unfortunately not. In very rare cases, doctors may be unable to safely insert a chest drain, perform a thoracoscopy, or complete a thoracoscopy which has been started. In addition, sometimes these procedures are completed successfully, but it is not possible or safe to give any talc. The risk of something like this happening would be the same for any patient, regardless of whether they are in a trial or not. Even if you are not able to undergo any of the trial procedures as planned, we shall still ask you to participate in trial measurements and follow-up appointments as any information you provide will still go towards our results, which may help people in the future. You will also continue to receive all of your normal medical care throughout the period of your trial involvement, which may include looking for alternative approaches to drain any fluid and manage your symptoms.

7. I am currently receiving chemotherapy/radiotherapy for my cancer. Will being in the trial affect my other treatments?

No. The treatments in the study do not affect the cancer itself, and neither do they interfere with anti-cancer therapies. The main aim of this trial is to determine the best way to manage pleural effusions, and the symptoms they cause.

8. If I take part in the trial, what will happen to me before I enter the trial?

Before your doctors consider you for the TAPPS trial, you will have been diagnosed with a malignant pleural effusion that is causing you symptoms, and is large enough to allow you to undergo a thoracoscopy if necessary. You and your doctor will have agreed that it is both appropriate and practical for you to have your fluid drained, and for you to have talc applied to try and prevent further fluid build-up. Before you are asked to undergo any trial-related procedures, you will be seen by one of the trial team who will explain the trial to you and give you the opportunity to ask any questions. You will then typically be given an appointment to come to hospital to receive the treatment, unless you are already an inpatient.

9. What will happen to me at the beginning of the trial?

Once you are admitted to hospital, or when it is appropriate if you are already an inpatient, you will be asked to sign a consent form to enter the trial if you are happy to do so. You should have had enough time, in your opinion, to read this information sheet and to fully consider participating in the trial. You will then have a consultation with a trial doctor who will ask questions about your treatment to date, your history and your symptoms. You will have an examination and may have a chest x-ray and blood tests taken. We shall also be asking for your permission to use some of the blood samples we take during the course of your trial involvement for analysis as part of the TAPPS trial, and for future research studies. Trial samples will be stored with a code number so that they are not directly identifiable to you. You will also be asked to fill out some health questionnaires. Following this, you will be randomised to undergo ONE of the two procedures described below, 'a' or 'b'. Your doctors and the trial team have no influence over which treatment you will receive, as this decision is made by a computer.

a. Chest drain and slurry. If you are allocated to this group, your doctors will place a small chest tube into your fluid under local anaesthetic. Your tube will be stitched in place and attached to a portable bottle to allow the fluid to drain away. The whole procedure shouldn't take more than half an hour. Once the fluid has drained away, which can take a day or two, a mixture consisting of saline (salt water) and the sterile talc powder will be injected through the tube. During the first 24 hours after the talc is injected, your drainage bottle may be attached to a gentle suction device which is on the wall by your bed. This may restrict the distance you can travel away from the bed, but gives the treatment the best chance of working. Once the amount of fluid draining from the tube has reduced sufficiently, the tube will be removed. On average, patients who undergo this kind of treatment are in hospital for around 5 to 7 days.

b. Thoracoscopy and poudrage. If you are allocated to this group, you will undergo a medical thoracoscopy (also known as local anaesthetic thoracoscopy, or LAT). A camera will be inserted through the chest wall under local anaesthetic to inspect the inside of your chest, with most of the fluid being removed through a small incision beforehand. Towards the end of the procedure, sterile talc powder will be sprayed into the chest to coat the lining of the lung. A chest tube will be inserted before being stitched in place and attached to a portable bottle. The whole procedure shouldn't take more than an hour. The bottle may be attached to a gentle suction device, which is on the wall by your bed, for the first 24 hours after the procedure. This may restrict the distance you can travel away from the bed, but gives the treatment the best chance of working. Once the amount of fluid draining from the tube has reduced sufficiently, the tube will be removed, with a small stitch left in place. On average, patients who undergo this kind of treatment are in hospital for around 2 to 3 days, with the stitch coming out about a week later.

We may also ask for your permission to store some of the pleural fluid which will be removed as part of your procedure, so it can be analysed in the same way as your blood samples. On the second day after your talc is given (or sooner if you are due to go home before then), you will have some more blood samples taken, although these ones will not be stored any longer than normal and will be processed quickly.

During your stay in hospital you will also be asked to fill out a simple chart which tells us how breathless you are, and how much pain you are in. This shouldn't take more than a few seconds each day. We shall ask you to complete these scores every day for the first 7 days after your procedure.

Finally, as part of the trial but regardless of which procedure you receive, you will have a chest x-ray about 24 hours after your procedure, and another one performed soon after your drain is removed, usually just before you leave hospital. Alongside these, you may have additional chest x-rays as part of your normal clinical care.

10. What will happen to me once I've left hospital?

Before you go home, you will be given a simple diary to record any contact you have with medical services after discharge. In addition to the diary, you will be asked to record your levels of

pain and breathlessness in much the same way as when you were in hospital. We shall provide you with a chart which will only need to be completed once a week.

Following discharge, you will be seen in clinic three times in total, after one month, after 3 months, and after 6 months. These visits will be specifically for the trial and won't necessarily replace any other appointments you may need, although we shall do everything possible to make them coincide with any other appointments you may have. At each of these visits you will be asked to have a chest x-ray, and to fill out some quality of life questionnaires as before. A member of the trial team will also see you to talk about how you are feeling and discuss your chart and your diary.

We may contact you over the telephone to remind you to attend follow-up appointments, or to complete the charts or diary, but only with your permission.

11. Information about talc

Talc is a naturally occurring soft powder which has been used in medicine for decades. It is given on a daily basis in hospitals all over the world, and its use is considered standard care in the UK. When inserted into the pleural space it acts as an irritant and has been shown to be the most effective substance for causing pleurodesis, which potentially stops fluid recurring. Medical talc is very carefully selected, and is completely sterilised before use. It is extremely safe, but patients can sometimes experience pain in the chest around the time it is inserted. You will usually be given painkillers before the procedure and be given local anaesthetic along with the talc. If you have had a reaction to local anaesthetic before then you should inform a member of the trial team. After talc insertion some people can develop a slight fever but this is often easily manageable with drugs such as paracetamol. All procedures carry a slight risk of infection, including the use of talc, although we shall minimise this risk by using sterile equipment.

12. Information about chest drains

Small chest drains are the mainstay of treatment for removing any substance which builds up around the lungs, including air, fluid and blood. They are regularly used as standard therapy in most hospitals and can be inserted quickly and safely under local anaesthetic, although there are a few minor risks associated with their use. On very rare occasions inserting them can cause damage to underlying structures, or can cause bleeding. These complications are extremely rare and can usually be avoided by guiding the placement of the chest tube with an ultrasound scan. All chest tubes in this trial will be placed using ultrasound. It is also theoretically possible for infection to occur following drain insertion, although this is kept to a minimum by using sterile techniques and equipment. Finally, some patients can experience discomfort with the tube in place. It is difficult to predict who this will affect but all patients will be given painkillers as needed.

13. Information about thoracoscopy

Thoracoscopy is performed in an increasingly large number of hospitals in the UK. All of the centres in this trial perform this procedure as part of their normal routine practice. Thoracoscopy can be used to help diagnose patients with pleural disease, as well as treat them, often at the same time. Medical thoracoscopy is usually done under light sedation and local anaesthetic and, as with any procedure, can carry some minor risks. Whilst performing

a thoracoscopy, it is possible to cause damage to the chest or to other structures within it (including the lung). This can usually be avoided by guiding the procedure with an ultrasound scan. All thorascopies in this trial will be performed using ultrasound. It is also possible for infection to be caused by the procedure, although this is kept to a minimum by performing it in a clean environment under sterile conditions. Finally, some patients may feel sore and bruised after the procedure, although this is typically easy to control with painkillers such as paracetamol or codeine, and only lasts for a few days.

14. What are the potential benefits from taking part?

We hope that every patient in the trial will benefit, as normal, from whichever treatment they receive as well as continued follow-up appointments. The main aims of both treatments are to remove pleural fluid and so reduce breathlessness, and to keep people well by preventing any more fluid returning.

Whichever group you are allocated to, your participation in this trial will contribute to our understanding of the best way to manage malignant pleural effusions, which will hopefully benefit patients like you in the future.

15. What are the possible disadvantages and risks of taking part?

You will have at least 6 chest x-rays during your participation in this study, although many of these would need to be done whether you were in the trial or not. There are some theoretical health risks from excessive radiation exposure, but chest x-rays are considered one of the safest tests as the dose from one is only equivalent to around four days' worth of normal background radiation.

We shall be monitoring you closely for the side effects explained in sections 11, 12 and 13. Apart from these side-effects, and your time commitment, there are no other likely disadvantages to taking part.

Please note that we shall always try to arrange your trial follow-up appointments along your routine clinic appointments to minimise the number of times you need to come to the hospital. If we cannot arrange this, you will be reimbursed for any extra travel expenses you may incur by attending a trial visit.

16. Will my medical information be kept confidential?

Yes, your medical records will be kept confidential but in order for the trial to run smoothly they may need to be looked at by certain groups of people, specifically:

- Key members of the research team, including those based at the trial co-ordinating centre (Oxford Respiratory Trials Unit, ORTU). The research team includes doctors and nurses who would usually be involved in your care, as well as the doctors, nurses and administrators who are co-ordinating the trial.
- Representatives of North Bristol NHS Trust who are sponsoring the trial and who must ensure the trial is run in a proper manner

All of these people have a duty of confidentiality to you as a research participant.

Information about you will be collected for analysis by the Sponsor's trial team at North Bristol NHS Trust, and other collaborators in the study. This will include information about your health and other details such as your age and your gender. This information will be stored on a secure database which is accessible only to the research team. Each patient will be allocated a personal study number as an identifier so there will be no record of names or contact details in the study database. Chest x-rays or CT scans which are performed during the period of your trial involvement (even those not performed as part of the trial) may also be collected and transferred to the trial team, although these will only be identifiable by your study number and not your personal details. However, with your permission, some identifiable details, such as your name, date of birth, address and NHS number may be transferred to the Sponsor's trial team and/or study co-ordinating centre (ORTU) either on paper or via fax. This will be done for the purpose of follow-up through the Health and Social Care Information Centre which will allow us to keep in touch with you and follow up your health status.

17. Stopping your participation in the trial

The study doctors may withdraw you from the trial at any time, if they feel that it is no longer safe or appropriate for you to continue.

North Bristol NHS Trust may also stop the trial early, although if this happens the reasons will be explained to you.

18. What if new information becomes available?

The trial team will continue to review all new research data. If new information that influences the trial becomes available, alterations will be made accordingly. If this changes your involvement in the trial, or how we handle your samples, then you will be contacted with an updated information sheet and asked to sign a further consent form. Your right to withdraw from the trial remains the same with there being no impact on your standard care.

19. What if there is a problem?

If you have any concerns, or are displeased about any aspect of this study or your wider care then we would encourage you to ask to speak to a trial doctor or nurse who will attempt to address any issues you may have. If you do not wish to speak to a member of the trial team, or if you remain unhappy and wish to make a formal complaint, then you can do this through your hospital's Advice and Complaints Team, whose contact information can be found below.

If you are harmed as a result of your participation in this study, due to someone's negligence, North Bristol NHS Trust will provide indemnity and / or compensation via the NHS indemnity scheme.

If you are harmed as a result of your participation in this study, but not due to negligence, North Bristol NHS Trust will sympathetically consider any claim for compensation.

20. Who is organising and funding the research?

North Bristol NHS Trust is sponsoring the research, which means that the trust has overall responsibility to ensure that the trial is conducted in a safe and appropriate manner.

The study has been funded by a research grant from the NIHR Health Technology Assessment (HTA) programme. More information about this can be found online at <http://www.hta.ac.uk>. No payment will be made to the trial doctors or nurses for including you in the study.

21. Who has reviewed and approved the trial?

In order to protect your rights, safety and dignity, this study has been reviewed and approved by the North West (Preston) Research Ethics Committee, as well as by the research department in your local NHS Trust.

22. What will happen to the results of the trial?

When the study has finished the results will be analysed. These will then be published in a medical journal so that other doctors can read them and learn from them. No identifiable patient information will be published. If you would like a copy of the medical paper, or would like us to write to you personally to explain the study findings then please indicate this on your consent form.

23. What will happen to the samples taken in the trial?

Many of the blood tests which are needed for the trial will be done as part of your standard care, but occasionally we may require one or two extra small vials of blood to be taken. We may also need to collect samples of pleural fluid, but these are taken from the drained fluid which would otherwise be thrown away. Some of the blood and pleural fluid samples collected will be kept by the trial team and analysed at a later date. Following this, some samples may be stored and used in future research studies, subject to ethical approval, with the aim of developing diagnostic tools and new treatments to help doctors treating patients like you. Some of these studies may be funded by commercial companies. We are asking you to consider these samples as a gift to the research team to help us with our research in the future.

All samples which need to be stored for trial purposes will be frozen and held securely in a "coded" form, meaning that each sample will be labelled with a number and not your name or date of birth, which protects your confidentiality. The list linking your name to the sample will be securely held separately, meaning that only members of the trial team will be able to link the samples back to you. If samples are used by other researchers, then you will not be identifiable by them.

24. Will any genetic tests be performed?

With your consent, we will perform genetic analysis on your samples which we hope will provide further information on your condition. These tests will look at why some people seem to get fluid around their lungs in association with cancer, and whether genetic differences may be a cause. The results will be used to try to understand this condition further in the future – they are not of direct use to you or your treatment. As the results of these tests do not change how you are looked after, we would not normally let you know the results, and we will not contact members of your family with the results either. **The samples will not be tested for chronic diseases or HIV, and will not be used for any genetic manipulation.**

25. What do I need to do now if I agree to participate?

If after reading this information sheet you have any questions about the trial, please ask a member of the trial team, whose contact details can be found below.

If you would like to take part then we shall ask you to sign a consent form, which will also ask if you want your GP to be informed of your involvement. If you would like extra time to consider entry into the trial, perhaps to discuss with your family or GP, then please let us know.

If you agree to participate in the trial you are free to withdraw at any time without giving a reason and without affecting your rights or medical care.

26. What happens if I decide not to participate?

If you decide not to participate, your routine medical care and your legal rights will not be affected in any way, and you will not be at any disadvantage over those people who do participate. Any decisions about how to manage your pleural fluid will be made in a normal manner between you and your doctor, who may recommend that you receive one of the above treatments, although not as part of the trial.

Thank you for taking the time to read this information, and for considering taking part in the TAPPS trial.

Contact details

Your local principal investigator is:	DR NICK MASKELL
For routine trial-related questions during working hours, please contact:	0117 323 5838
If applicable, for out of hours trial-related questions please contact:	
For further information about research and clinical trials in your local area, please contact:	Research & Innovation North Bristol NHS Trust Floor 3 Learning & Research building Southmead Hospital Westbury-on-Trym Bristol BS10 5NB Telephone: 0117 32 36468 Email: research@nbt.nhs.uk
To speak to your local hospital's Advice and Complaints Team, please contact:	Advice & Complaints Team (ACT) Beaufort House Beaufort Way Southmead Hospital Southmead Bristol BS10 5NB Tel: 0117 323 3741 Email: complaints@nbt.nhs.uk

For any emergency or non-trial-related issues please contact medical services as per normal.

TAPPS TRIAL – PATIENT CONSENT FORM

PLEASE COMPLETE OR AFFIX PATIENT LABEL
NHS NUMBER
DATE OF BIRTH
ADDRESS

Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial)
 Chief Investigator: Dr Nick Maskell
 REC 12/NW/0467

Trial number			

Recruiting centre

Please INITIAL in boxes

1	I confirm that I have read and understood the patient information sheet dated/...../..... (Version) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered to my satisfaction.	
2	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my future medical care or legal rights being affected as a consequence.	
3	I give permission for samples of my blood and pleural fluid to be taken, stored and analysed for the purposes of the TAPPS trial.	
4	I give permission for samples of my blood and pleural fluid to be stored and used in future research projects subject to ethical review.	
5	I understand that sections of my medical notes, and data collected during the study, may be looked at by individuals involved in the running of the trial, by regulatory authorities, or by representatives of North Bristol NHS Trust or the trial coordinating centre. I give permission for these individuals to have access to my records where it is relevant to my taking part in the research.	
6	I give permission for any anonymised radiological images obtained during my period of trial involvement, and for my trial data (some of which may identify me) to be transported from my hospital site to the sponsor site (North Bristol NHS Trust) or to the trial co-ordinating (the Oxford Respiratory Trials Unit) for the purposes of analysis, monitoring and follow up.	
7	I give permission for information about me, held by the NHS, the Health and Social Care Information Centre, and the NHS Central Register to be used to help provide information about my health status and to help contact me if necessary.	
8	I give permission to be contacted by members of the trial team by telephone, or by other means such as text or email, regarding the above study. I understand that my contact details will not be made available to any third parties.	
9	I would like my GP (Dr.....) to be notified about my participation in the study and I give my permission for you to contact them.	
10	I agree to take part in this study.	
If you would like to know the results of this study, please tick this box and we will write to you when the study is completed.		

		DD	MM	YYYY
Patient name (please PRINT)	Signature	Date		

		DD	MM	YYYY
Researcher completing form	Signature	Date		

TAPPS TRIAL – GENETIC CONSENT FORM

Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial)

Chief Investigator: Dr Nick Maskell
REC 12/NW/0467

Trial number			

Recruiting centre

As we expect to do some gene studies on the blood samples from this trial, we need to ask you to confirm your consent to this by signing this signature sheet as well as the general consent form.

These samples will be used to study which genes are important in conditions like yours, to help us understand exactly what happens in these diseases. Some of the genetic tests will try and clarify why some people, like you, develop these problems. The blood and gene samples may also be used in other research (some of which may be funded by commercial companies) with a view to developing medical diagnostic tools for doctors, and new treatments to help patients like you in the future.

The blood samples for gene testing will be stored at the Respiratory Research Unit at Southmead Hospital, Bristol. All this research will be done on coded samples, which protects your confidentiality.

If you are happy for us to use your samples in this way **please initial the box** before signing and dating below. Thank you for your time.

I agree to the collection and storage of blood and DNA (genetic) samples and for these to be used in future research, subject to ethical review

--

		DD	MM	YYYY
Patient name (please PRINT)	Signature	Date		

		DD	MM	YYYY
Researcher completing form	Signature	Date		

<p>ORTU & North Bristol NHS Trust</p>	<p>TAPPS DRAIN INSERTION AND SLURRY INSTILLATION</p>	<p>Page 1 of 4</p>
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North Bristol
NHS Trust

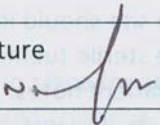


Oxford Respiratory Trials Unit

**TRIAL SPECIFIC PROCEDURE
FOR
TAPPS**

**TSP TAPPS 01.01
DRAIN INSERTION AND SLURRY INSTILLATION**

Effective date: 10th Oct 2012

Authored by	Name Dr Rahul Bhatnagar	Title Clinical Research Fellow
Reviewed by	Name Natalie Zahan	Title Research Nurse
Authorised by	Name Dr Nick Maskell	Title Consultant and Senior Lecturer in Respiratory Medicine
	Signature 	Date 10/10/12

<p>ORTU & North Bristol NHS Trust</p>	<p>TAPPS</p> <p>DRAIN INSERTION AND SLURRY INSTILLATION</p>	<p>Page 2 of 4</p>
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1 INTRODUCTION AND SCOPE

The purpose of the Trial Specific Procedure is to describe the procedures relating to drain insertion and slurry instillation for the purpose of the TAPPS study. It applies to researchers taking part in the TAPPS study and performing the above procedures as per protocol and the delegation log.

2 DEFINITIONS

There are no definitions for this TSP.

3 PROCEDURE

3.1. Drain insertion

1. Procedure ideally to be performed in dedicated clean environment (e.g. theatre, procedure room, etc.).
2. Explain procedure.
3. Obtain written consent for Seldinger drain insertion.
4. Position patient and administer sedation as necessary.
5. Perform thoracic ultrasound to confirm safe site for drain insertion.
6. Prepare kit, including filling drainage bottle to pre-marked prime line.
7. Don sterile gown and gloves, and sterilise insertion site using appropriate skin preparation.
8. Infiltrate local anaesthetic to skin and down to pleura.
9. Insert 10-14 French chest drain, using Seldinger technique.
10. Attach the provided 3-way adaptor to the drain, and screw in the tubing adaptor.
11. Secure to the skin.
12. Apply a small amount of gauze padding around the drain insertion site to prevent discomfort.
13. Fix to the skin using clear dressings. The insertion site should ideally be visible.
14. Attach the drain to the underwater seal using the sterile tubing provided.
15. Fully document procedure and drainage plan in patient notes.
16. Ensure the patient is prescribed adequate analgesia, and intrapleural flushes to maintain drain patency (20mls 0.9% saline three times daily).
17. Observations, including drainage volumes, should be performed at least every hour for the two hours post-insertion, reverting to standard frequency if there are no significant complications.
18. A chest x-ray should be performed to ensure adequate positioning.

<p>ORTU & North Bristol NHS Trust</p>	<p>TAPPS DRAIN INSERTION AND SLURRY INSTILLATION</p>	<p>Page 3 of 4</p>
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3.2 Drainage plan

1. Clamp / close the drain once 1000mls is reached, or if the patient experiences distress during drainage, or once one hour has passed post-insertion.
2. Ensure the drain is clamped / closed for a minimum of 1 hour before further drainage is allowed.
3. Drainage volumes are to be charted at least every 8 hours for the duration of drain use.

3.3 Talc slurry pleurodesis

1. Procedure may be performed at the patient's bedside as long as aseptic technique is maintained.
2. Explain procedure.
3. Administer pre-medication (e.g. 10mg oral morphine solution).
4. Position the patient comfortably, allowing access to the drain.
5. Expose the 3-way tap.
6. Clean the access port using an alcohol-based swab.
7. Instil 10mls of sterile 0.9% saline into the pleural cavity via the 3-way tap, to ensure drain patency.
8. Instil 3mg/kg (maximum 250mg) of 1% lidocaine in to the pleural space via the 3-way tap.
9. Turn the tap off to the drain (clamp) for 10 minutes.
10. Make up 4 grams of sterile talc to a slurry using 50mls of 0.9% sterile saline.
11. Instil the slurry in to the pleural cavity via the 3-way tap at least 10 minutes after lidocaine instillation.
12. Flush 20mls of 0.9% saline into the pleural cavity via the 3-way tap.
13. Turn the tap off to the drain (clamp) for 2 hours.
14. Re-open the 3-way tap to both the drain and the drainage bottle.
15. Apply thoracic suction (-10 to -20cmH₂O) for at least 24 hours.
16. Ensure the patient is prescribed adequate analgesia.
17. Observations should be performed every 15 minutes for the first hour post-talc, then hourly for the next 3 hours, before reverting to standard frequency if there are no significant complications.
18. A chest x-ray should be performed between 18 and 24 hours post talc instillation.

3.4 Post-pleurodesis

1. Drains should remain in place for at least 24 hours post talc slurry instillation.
2. Drainage volumes should continue to be recorded at least every 8 hours.
3. Once drainage volumes fall below 250mls in the preceding 24h hours the drain may be removed.
4. A PA chest x-ray should be performed prior to the patient being discharged home.

<p>ORTU & North Bristol NHS Trust</p>	<p>TAPPS DRAIN INSERTION AND SLURRY INSTILLATION</p>	<p>Page 4 of 4</p>
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4 ASSOCIATED FORMS

There are no forms associated with this TSP.

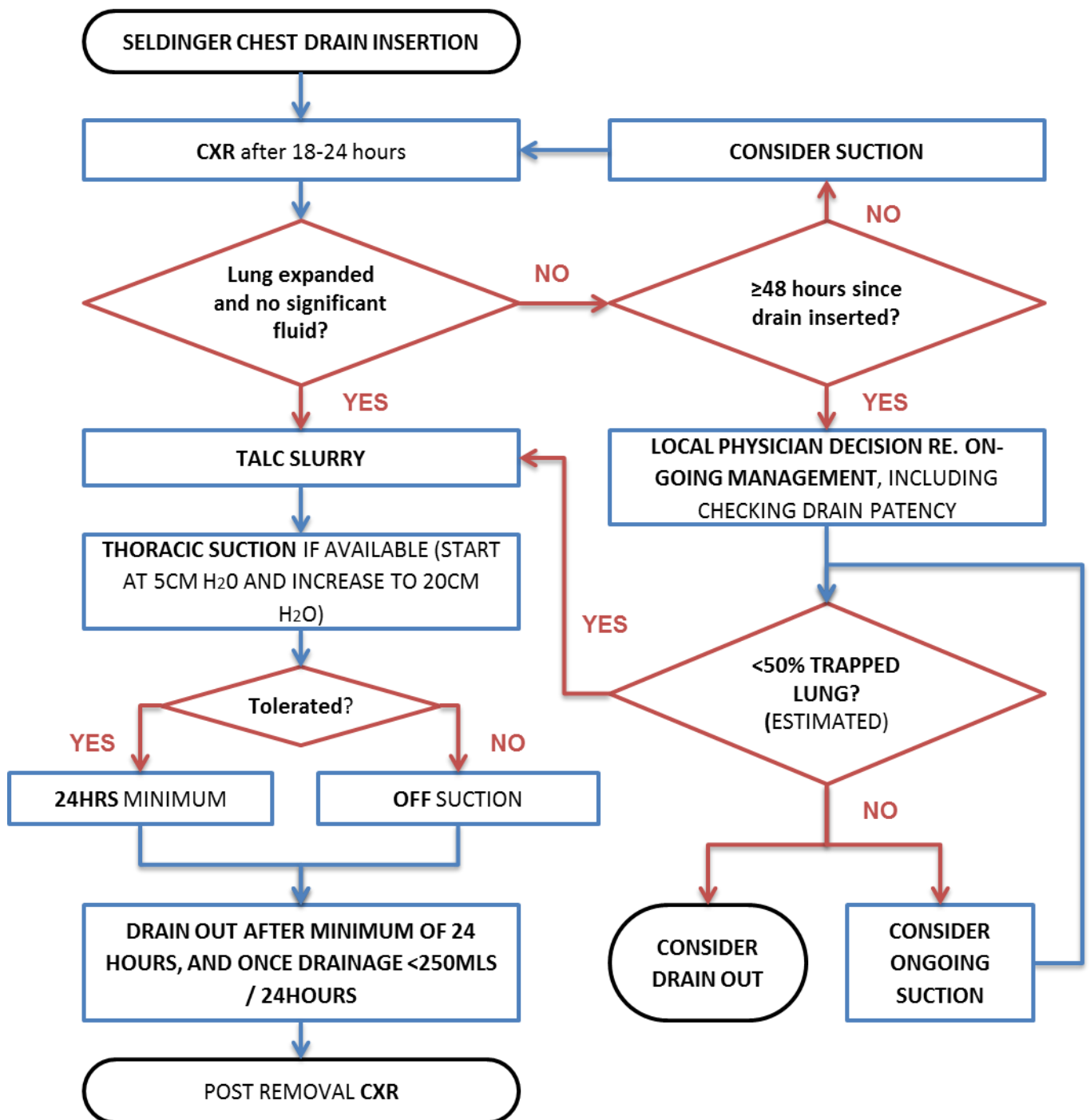
5 REVISION HISTORY

SOP No	Effective date	Revision summary
01.01	10/Oct/2012	New TSP

6 APPENDICES

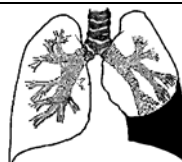
There are no appendices for this TSP.

APPENDIX 5 – TREATMENT FLOW CHART FOR SLURRY ARM



<p>ORTU & North Bristol NHS Trust</p>	<p>TAPPS TSP TAPPS 03.01 MEDICAL THORACOSCOPY & POUDRAGE</p>	<p>Page 1 of 3</p>
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North Bristol
NHS Trust



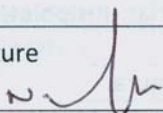
Oxford Respiratory Trials Unit

**TRIAL SPECIFIC PROCEDURE
FOR
TAPPS**

TSP TAPPS 03.01

**MEDICAL THORACOSCOPY & POUDRAGE
(INTERVENTION ARM)**

Effective date: 10th Oct 2012

Authored by	Name Dr Rahul Bhatnagar	Title Clinical Research Fellow
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1 INTRODUCTION AND SCOPE

The purpose of the Trial Specific Procedure is to describe the procedures relating to thoracoscopy and poudrage for the purpose of the TAPPS study. It applies to researchers taking part in the TAPPS study and performing the above procedures as per protocol and the delegation log.

2 DEFINITIONS

There are no definitions for this TSP.

3 PROCEDURE

3.1 Thoracoscopy and poudrage

Please also refer as needed to the British Thoracic Society Pleural Disease Guideline 2010 on Local Anaesthetic Thoracoscopy (Appendix – A Practical Guide to the Procedure).

1. Procedure ideally to be performed in dedicated theatre, endoscopy suite or 'clean environment' (e.g. dedicated procedure room).
2. Explain procedure.
3. Obtain written consent for medical thoracoscopy.
4. Position patient and administer sedation as necessary.
5. Perform thoracic ultrasound to confirm safe site for port insertion.
6. Prepare kit, including filling drainage bottle to pre-marked prime line.
7. Don sterile gown and gloves, and sterilise insertion site using appropriate skin preparation.
8. Infiltrate local anaesthetic to skin and down to pleura.
9. Make adequate skin incision.
10. A closing suture should be placed either at this point, or towards the end of the procedure.
11. Create port site by dissecting down to pleura.
12. Insert trocar and port before removing trocar to leave port in-situ.
13. Aspirate chest cavity to dryness using flexible suction catheter. Record total drainage volume.
14. Perform thoracoscopy, including visual survey of chest cavity; pleural fluid collection; targeted biopsies as necessary; and breakdown of minor adhesions if safe to do so.
15. At the end of the procedure spray 4 grams of sterile talc over the pleural surface using a poudrage kit, aiming for an even spread of talc. Ensure that there is

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enough space left around the delivery tube/needle to allow air to escape (to avoid inducing a tension pneumothorax).

16. Remove the thoracoscopy port and insert a 16 – 24 French chest drain via the port tract.
17. Secure drain in place and apply appropriate dressings.
18. Consider attaching a chest drain adaptor (e.g. Thal-Quick Chest Tube Adaptor) to allow easy pleural access without disconnecting the drain.
19. Attach to an underwater drainage bottle using sterile tubing.
20. Admit to ward and ensure adequate analgesia is prescribed.
21. Connect to thoracic suction for at least 24 hours.
22. A chest x-ray should be performed to ensure adequate drain positioning.
23. The drain should stay in place for at least 24 hours post-poudrage.

3.2 Post-thoracoscopy

1. Observations (pulse, temperature, blood pressure, saturations, and respiratory rate should be performed every 15 minutes for the first hour post-procedure, then hourly for the next 3 hours, before reverting to standard frequency if there are no significant complications.
2. A chest x-ray should be performed between 18 and 24 hours post-poudrage.
3. Drainage volumes should be recorded at least every 8 hours.
4. Once drainage volumes fall below 250mls in the preceding 24h hours the drain may be removed.
5. A PA chest x-ray should be performed prior to the patient being discharged home.

4 ASSOCIATED FORMS

There are no forms associated with this TSP.

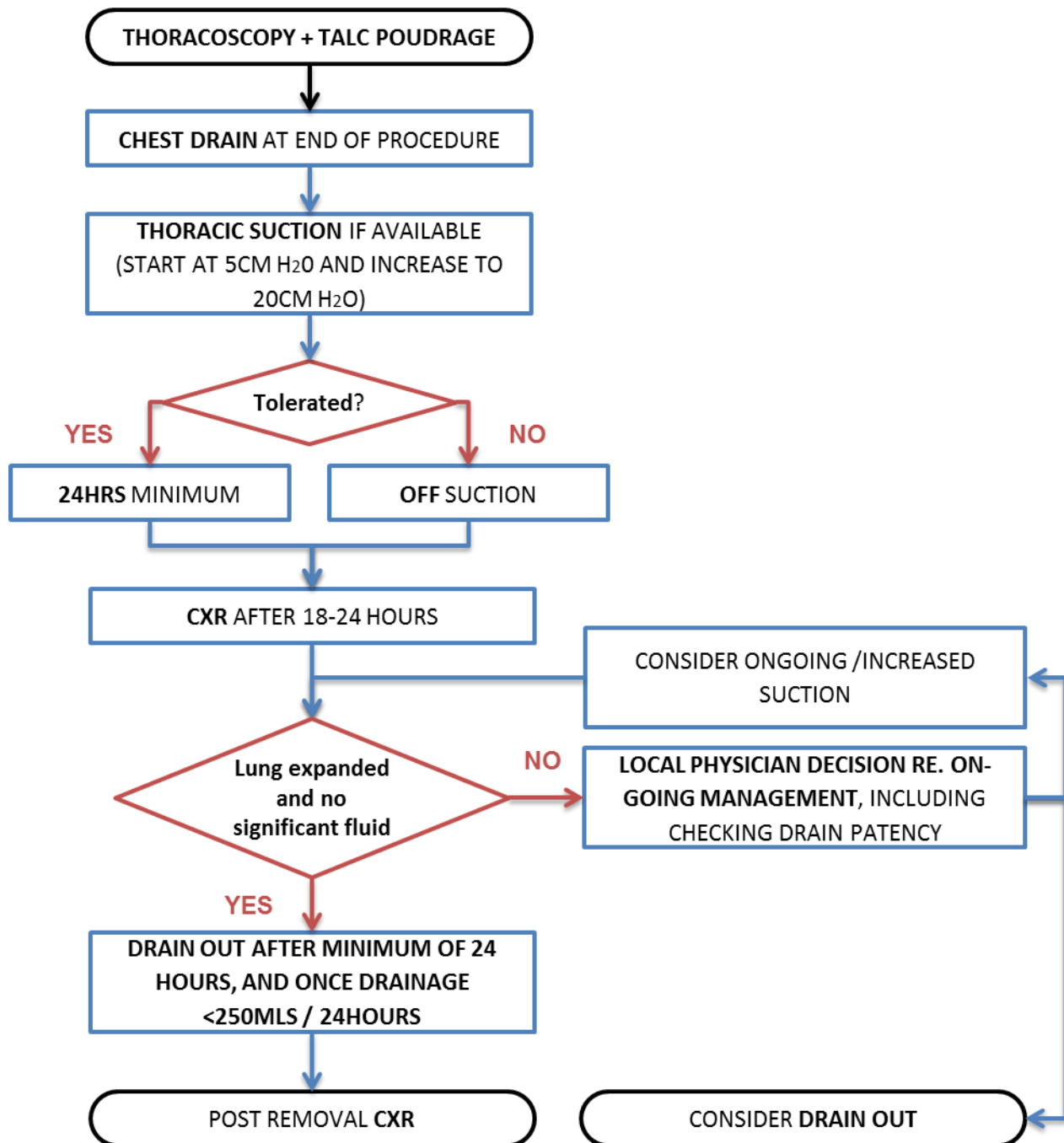
5 REVISION HISTORY

SOP No	Effective date	Revision summary
03.01	10/Oct/2012	New TSP

6 APPENDICES

There are no appendices associated with this TSP.

APPENDIX 7 – TREATMENT FLOW CHART FOR POUDRAGE ARM



APPENDIX 8 – OVERVIEW OF PROTOCOL AMENDMENTS

Amendment number	Details of significant alterations to protocol	Resulting protocol version and date
1	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Adjustments to the follow up visit windows • Administrative details were updated throughout the protocol. 	3.0 14/08/2013
4	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Edited the safety reporting section of the protocol • Updated administrative details throughout the protocol • Added appendix 6 	5.0 01/06/2014
7	<ul style="list-style-type: none"> • 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