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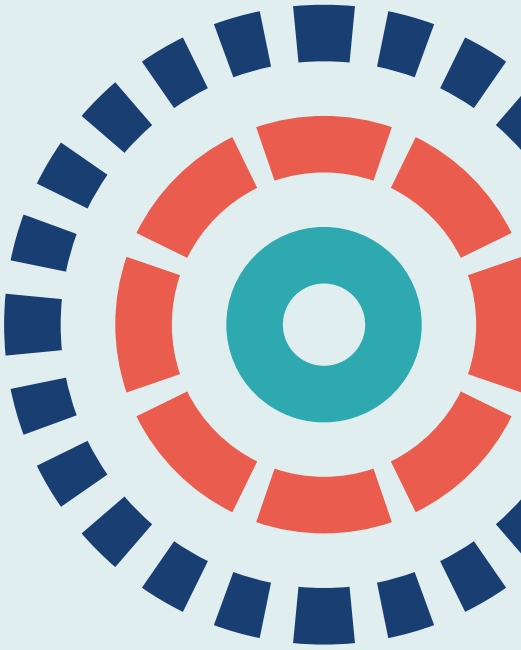

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Thoracoscopy and talc poudrage compared with intercostal drainage and talc slurry infusion to manage malignant pleural effusion: the TAPPS RCT

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Abstract

Thoracoscopy and talc poudrage compared with intercostal drainage and talc slurry infusion to manage malignant pleural effusion: the TAPPS RCT

Rahul Bhatnagar,[1] Ramon Luengo-Fernandez,[2] Brennan C Kahan,[3] Najib M Rahman,[4] Robert F Miller[5] and Nick A Maskell[1]*

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Background: There are around 40,000 new cases of malignant pleural effusion in the UK each year. Insertion of talc slurry via a chest tube is the current standard treatment in the UK. However, some centres prefer local anaesthetic thoracoscopy and talc poudrage. There is no consensus as to which approach is most effective.

Objective: This trial tested the hypothesis that thoracoscopy and talc poudrage increases the proportion of patients with successful pleurodesis at 3 months post procedure, compared with chest drain insertion and talc slurry.

Design: This was a multicentre, open-label, randomised controlled trial with embedded economic evaluation. Follow-up took place at 1, 3 and 6 months.

Setting: This trial was set in 17 NHS hospitals in the UK.

Participants: A total of 330 adults with a confirmed diagnosis of malignant pleural effusion needing pleurodesis and fit to undergo thoracoscopy under local anaesthetic were included. Those adults needing a tissue diagnosis or with evidence of lung entrapment were excluded.

Interventions: Allocation took place following minimisation with a random component, performed by a web-based, centralised computer system. Participants in the control arm were treated with a bedside chest drain insertion and 4 g of talc slurry. In the intervention arm, participants underwent local anaesthetic thoracoscopy with 4 g of talc poudrage.

Main outcome measures: The primary outcome measure was pleurodesis failure at 90 days post randomisation. Secondary outcome measures included mortality and patient-reported symptoms. A cost–utility analysis was also performed.

Results: A total of 166 and 164 patients were allocated to poudrage and slurry, respectively. Participants were well matched at baseline. For the primary outcome, no significant difference in pleurodesis failure was observed between the treatment groups at 90 days, with rates of 36 out of 161 (22%) and 38 out of 159 (24%) noted in the poudrage and slurry groups, respectively (odds ratio 0.91, 95% confidence interval 0.54 to 1.55; $p = 0.74$). No differences (or trends towards difference) were noted in adverse events or any of the secondary outcomes at any time point, including pleurodesis failure at 180 days

[poudrage 46/161 (29%), slurry 44/159 (28%), odds ratio 1.05, 95% confidence interval 0.63 to 1.73; $p = 0.86$], mean number of nights in hospital over 90 days [poudrage 12 nights (standard deviation 13 nights), slurry 11 nights (standard deviation 10 nights); $p = 0.35$] and all-cause mortality at 180 days [poudrage 66/166 (40%), slurry 68/164 (42%); $p = 0.70$]. At £20,000 per quality-adjusted life-year gained, poudrage would have a 0.36 probability of being cost-effective compared with slurry.

Limitations: Entry criteria specified that patients must be sufficiently fit to undergo thoracoscopy, which may make the results less applicable to those patients presenting with a greater degree of frailty. Furthermore, the trial was conducted on an open-label basis, which may have influenced the results of patient-reported measures.

Conclusions: The TAPPS (evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry) trial has robustly demonstrated that there is no additional clinical effectiveness or cost-effectiveness benefit in performing talc poudrage at thoracoscopy over bedside chest drain and talc slurry for the management of malignant pleural effusion.

Trial registration: Current Controlled Trials ISRCTN47845793.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 26. See the NIHR Journals Library website for further project information.

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Supplementary material has been provided by the authors to support the report and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

List of abbreviations

A&E	accident and emergency
AE	adverse event
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CXR	chest X-ray
ECOG	European Cooperative Oncology Group
EQ-5D	EuroQol-5 Dimensions
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
HRG	Healthcare Resource Group
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPC	indwelling pleural catheter
IQR	interquartile range
ISRCTN	International Standard Randomised Controlled Trial Number
LAT	local anaesthetic thoracoscopy
MPE	malignant pleural effusion
NICE	National Institute for Health and Care Excellence
OR	odds ratio
PI	principal investigator
QALY	quality-adjusted life-year
RCT	randomised controlled trial
SAE	serious adverse event
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-36	Short Form questionnaire-36 items
TAPPS	evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry
TSC	Trial Steering Committee
VAS	visual analogue scale
VATS	video-assisted thoracoscopic surgery
WHO	World Health Organization

Plain English summary

In patients with cancer, fluid can build up in the space between the chest wall and lung, causing breathlessness. The fluid can be drained using a small tube inserted between the ribs under local anaesthetic. However, it often recurs. To avoid this, doctors usually inject talc powder (mixed into a slurry) back down the drainage tube to try to 'stick' the lung to the inside of the chest wall. If successful, this prevents the fluid reforming. This procedure is called pleurodesis.

An alternative is to insert a camera into the chest under light sedation and local anaesthetic (a 'thoracoscopy') and spray talc directly onto the inside of the chest wall (poudrage). This may be more effective, although this has not been proven and it is a slightly more complex procedure.

Therefore, this trial was conducted to see if poudrage was more effective than slurry. A total of 330 patients were recruited from 17 UK hospitals who had chest fluid due to cancer. They were divided evenly, with half receiving standard drainage and slurry and the other half receiving a thoracoscopy and poudrage. They were followed up for 6 months. We measured how many experienced a recurrence in fluid build-up 3 months after treatment, as well as other impacts, including if there was any difference in the long-term costs.

No difference in clinical effectiveness was found between talc poudrage and talc slurry. Poudrage was unlikely to be cost-effective.

In summary, the researchers conclude that slurry is likely to be the preferable method.

Scientific summary

Background

Data suggest that there are around 40,000 new cases of malignant pleural effusion in the UK each year. Malignant pleural effusion is usually a result of a metastatic process and patient survival is typically poor. In general, average survival is quoted as being 4–6 months from diagnosis, although these data are drawn from highly heterogeneous patient groups. In addition, there are a number of factors that appear to influence survival, meaning that this figure may be less applicable to a number of patients. The underlying cancer type, in particular, appears to exert a strong influence on outcome, with some series reporting that those patients with mesothelioma (12 months) or breast cancer (> 2 years) survived longer.

For many patients, malignant pleural effusion can lead to debilitating symptoms, such as breathlessness or chest pain. Therapeutic aspiration of pleural fluid can lead to rapid relief for patients and is readily performed in the outpatient setting, although the volumes that can be removed in a single sitting are limited by the potential adverse effects of rapid, high-volume lung re-expansion. For this reason, thoracocentesis is usually considered to be a temporising measure rather than a definitive treatment, with recurrent aspirations reserved for those patients with a very short life expectancy. Indwelling pleural catheters are an increasingly used option, but this method of repeated drainage does not prevent fluid formation reliably, as recent data suggest that this occurs in approximately 20% of cases when drained at a typical frequency.

The more traditional and established approach to malignant pleural effusion treatment, pleurodesis, entails an attempt at preventing further fluid formation. This begins with emptying the chest of as much fluid as possible, which is usually accomplished following insertion of an intercostal chest drain (at the bedside under local anaesthetic) or during a thoracoscopic procedure (which may be performed under either light sedation or general anaesthesia). Once the pleural cavity is evacuated, an irritant is applied to the pleural linings with the intention of stimulating a local inflammatory response, resulting in fibrosis and adhesion (effectively obliterating the pleural space and, hopefully, preventing any further effusion formation). The primary perceived benefit of the pleurodesis approach is that a single intervention period can lead to long-term fluid prevention; a number of small series have described success rates in excess of 80%.

Talc slurry via chest tube is the current standard treatment approach for pleurodesis in the UK. This method has become ubiquitous as it is easily undertaken in the ward setting, with chest drain insertion possible at the bedside and not typically requiring anything other than local anaesthesia. Talc poudrage requires the capability to perform a thoracoscopy and for the patient to be able to tolerate such a procedure. Thoracoscopy may be undertaken by surgeons under general anaesthetic (video-assisted thoracoscopic surgery) or, as is increasingly the case in the UK, under light sedation (local anaesthetic thoracoscopy), the latter usually being performed by respiratory physicians in a dedicated procedural environment.

There is currently no consensus as to which approach is best. To the best of our knowledge, the largest study addressing the question of talc delivery for pleurodesis was performed by Dresler *et al.* and reported in 2005 (Dresler CM, Olak J, Herndon JE, Richards WG, Scalzetti E, Fleishman SB, *et al.* Phase III intergroup study of talc poudrage vs talc slurry sclerosis for MPE. *Chest* 2005;**127**:909–15). After withdrawals and exclusions, a total of 482 patients (slurry, $n = 240$; poudrage, $n = 242$) were included in the final analysis. Based on intention to treat, no significant difference was found between the two arms at 30 days. Following a per-protocol analysis, whereby patients with trapped lung were excluded, a significant difference ($p = 0.045$) was found, favouring poudrage, although this effect disappeared when only patients who were alive at 30 days (slurry, $n = 130$; poudrage, $n = 152$) were included.

Although undoubtedly important, the Dresler *et al.* 2005 study has not defined practice, as it was felt to have encompassed several potentially important flaws and barriers to wider generalisability, particularly in the UK. With the benefit of hindsight, these included a lack of detail regarding how randomisation, concealment or powering of the trial occurred; the use of ungraded talc; the use of video-assisted thoracoscopic surgery and general anaesthetic; the lack of an economic evaluation to inform broader utility and cost-effectiveness; poor retention to follow-up; major differences in treatment arms, such as assessing trapped lung using radiology in the slurry arm and intraoperatively in the other; no attempt at stratification prior to randomisation; the use of post hoc analyses to draw and report study conclusions; and, perhaps most importantly, a lack of what may be seen to be a clinically relevant or patient-centred definition of pleurodesis success.

How best to deliver talc into the pleural space remains an unanswered but important question, with the relatively poor-quality data described in the sections above failing to provide robust evidence to drive standardised clinical practice. This is particularly the case in the UK, where the pleurodesis approach offered will often be based on the individual preferences or beliefs of the treating clinician and the locally available facilities.

Objectives

The evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry (TAPPS) trial aimed to be the first adequately powered, robustly designed trial comparing the efficacy of talc poudrage (administered using local anaesthetic thoracoscopy) with the current standard treatment of a chest drain followed by talc slurry, for the management of patients with MPE in the UK.

The primary research question was, for patients with a confirmed malignant pleural effusion 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?

Methods

Design

This was a pragmatic, multicentre, UK-based, open-label, randomised controlled trial. A within-trial economic evaluation was conducted to assess the cost-effectiveness of both approaches. The TAPPS trial was given initial ethics approval by the National Research Ethics Service Committee (reference number 12/NW/0467), sponsored by North Bristol NHS Trust and jointly managed by research teams based at the University of Bristol and University of Oxford.

Inclusion criteria were as follows:

- a clinically confident diagnosis of MPE requiring pleurodesis, defined as –
    - pleural effusion with histocytologically proven pleural malignancy, or
    - pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid, or
    - pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging without a clear alternative cause for fluid
- fit enough to undergo local anaesthetic thoracoscopy
- expected survival > 3 months
- written, informed consent to trial participation.

Exclusion criteria were as follows:

- patients in whom thoracoscopy is the only reasonable approach to making a diagnosis and in whom such a diagnosis would significantly influence further management
- aged < 18 years
- females who are pregnant or lactating
- evidence of extensive lung entrapment on chest radiography or computed tomography, or significant fluid loculation on thoracic ultrasound, to a level that would normally be a contraindication to attempted talc pleurodesis
- insufficient volume or position of pleural fluid on lateral decubitus thoracic ultrasound to safely perform local anaesthetic thoracoscopy without further intervention being necessary
- previously documented adverse reaction to talc
- clear contraindication to thoracoscopy or chest tube insertion.

Sample size

Previous literature and local audit data suggested that patients with a World Health Organization 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.

Thus, 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, a total of 325 patients was required.

The final recruitment target was rounded up to 330 patients, with 165 patients to be allocated equally to each treatment arm.

No interim analyses were planned.

Consent and treatment allocation

All patients provided informed consent to trial entry. Patients were randomly assigned, in a 1 : 1 ratio, to one of the trial treatments. Randomisation was performed centrally by the trial management team in Oxford, using a computer-based system. Minimisation with a random element was utilised. The minimisation factors were type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other) and World Health Organization performance status (0–1, 2–3).

Because of the inherent and substantial differences between the two methods being tested, this trial could not be performed ethically or safely in a blinded manner using dummy or sham procedures.

Trial treatments

Participants allocated to the control group underwent 12–14 French gauge chest drain insertion and were then administered 4 g of sterile talc slurry. Drain removal and consideration for discharge occurred once < 250 ml of fluid output was recorded in a 24-hour period.

Participants allocated to the intervention group underwent local anaesthetic thoracoscopy and talc poudrage with 4 g of sterile talc slurry and insertion of a 16–24 French gauge chest drain at the end of the procedure. After a minimum of 24 hours, drain removal and consideration for discharge occurred once < 250 ml of fluid output was recorded in a 24-hour period.

Follow-up period

Trial follow-up appointments took place at 1 month (day 28 ± 7 days), 3 months (day 84 ± 10 days) and 6 months (168 days ± 14 days) post randomisation.

Outcome measures

The primary end point was the number of patients who experienced pleurodesis failure up to 3 months (90 days) post randomisation.

A patient was defined was experiencing pleurodesis failure if they underwent a therapeutic procedure on the side ipsilateral to their trial intervention, or if this procedure was needed but not performed.

A range of secondary outcomes as also assessed, including patient-reported symptoms and quality of life, pleurodesis failure rates at 30 and 180 days, and mortality.

Cost-effectiveness was assessed taking into account quality-adjusted life-years and resource use during the initial procedure and over the trial period.

Results

Recruitment took place between August 2012 and October 2017, with 17 centres contributing participants.

The target of 330 patients was achieved, with 164 allocated to the control (slurry) arm and 166 to the intervention (poudrage) arm. A total of 159 (97%) and 161 (97%) patients from the control and intervention arms, respectively, were included in the primary outcome analysis. Fourteen (8.5%) and 15 (9.0%) patients from the control and intervention arms, respectively, withdrew during the 6-month follow-up period. The treatment groups were well matched at baseline.

Primary outcome

For the primary outcome, no significant difference in pleurodesis failure was observed between the treatment groups at 90 days, with rates of 36 out of 161 (22%) and 38 out of 159 (24%) noted in the poudrage and slurry groups, respectively (odds ratio 0.91, 95% confidence interval 0.54 to 1.55; $p = 0.74$).

Secondary outcomes

No differences (or trends towards difference) were noted in any of the secondary outcomes at any time point, including pleurodesis failure at 30 days [poudrage 16/161 (10%), slurry 22/159 (14%), odds ratio 0.69, 95% confidence interval 0.34 to 1.37; $p = 0.29$]; pleurodesis failure at 180 days [poudrage 46/161 (29%), slurry 44/159 (28%), odds ratio 1.05, 95% confidence interval 0.63 to 1.73; $p = 0.86$]; mean number of nights in hospital over 90 days [poudrage 12 nights (standard deviation 13 nights), slurry 11 nights (standard deviation 10 nights); $p = 0.35$]; all-cause mortality at 180 days [poudrage 66/166 (40%), slurry 68/164 (42%); $p = 0.70$]; thoracic pain ($p = 0.69$, $p = 0.61$, $p = 0.85$ and $p = 0.78$ at days 7, 30, 90 and 180, respectively); dyspnoea ($p = 0.51$, $p = 0.20$, $p = 0.58$ and $p = 0.41$ at 7, 30, 90 and 180 days, respectively); or percentage radiographic opacification ($p = 0.66$, $p = 0.58$, $p = 0.45$ and $p = 0.79$ at drain removal, at 30, 90 and 180 days, respectively).

Adverse events

There was no significant difference between the groups in the number of adverse events or serious adverse events recorded at 7, 30 or 180 days. A total of 179 and 152 adverse events were recorded in the intervention and control arms, respectively. The most commonly seen adverse events were worsening dyspnoea due to disease-related fluid (poudrage, $n = 23$; slurry, $n = 20$), pneumothorax or bronchopleural fistula (poudrage, $n = 15$; slurry, $n = 18$) and pneumonia or chest infection (poudrage, $n = 25$; slurry, $n = 19$).

Cost-effectiveness

The mean total NHS and hospice care costs were £10,146 (95% confidence interval £9119 to £11,212) for patients randomised to standard chest tube talc slurry pleurodesis and £10,687 (95% confidence interval £9621 to £11,627) for patients randomised to thoracoscopy-delivered talc poudrage, a mean difference of £541 (95% confidence interval difference –£953 to £1933). The mean quality-adjusted life-year gain was 0.239 in the standard chest tube talc slurry pleurodesis group and 0.246 in the thoracoscopy-delivered talc poudrage group, a mean difference of 0.007 quality-adjusted life-years (95% CI –0.019 to 0.034). Therefore, the incremental cost per quality-adjusted life-year gained when poudrage was compared with slurry was £77,286. At the conventional £20,000 per quality-adjusted life-year gained threshold, thoracoscopy-delivered talc poudrage would have a 0.36 probability of being cost-effective.

Conclusions

The results of the TAPPS trial appear to be conclusive, in that there was no evidence of any difference between the two treatment arms in the primary outcome measure: pleurodesis failure at 90 days post randomisation. Indeed, no significant difference or trend towards difference was noted in any of the secondary outcome measures, including pleurodesis failure up to the final follow-up visit at 180 days post randomisation, mortality, time spent in hospital, radiological appearances or patient-reported outcomes. Absolute values for pleurodesis failure were low (approximately 23% in both arms) at 90 days and this was maintained for the duration of the trial (approximately 30% in both arms at 180 days). The health economic analysis suggested that talc poudrage has a low probability (36%) of being cost-effective when compared with talc slurry.

To the best of our knowledge, the TAPPS trial is the first randomised controlled trial to examine the efficacy of talc poudrage delivered at LAT compared with traditional talc slurry. It addresses a clear and important area of uncertainty in clinical practice and has been able to inform this definitively. The trial processes, including randomisation and treatment allocations, were robustly designed, with the likelihood of bias minimised as far as possible. The trial interventions were performed in a standardised fashion that was reflective of current practice, meaning the results are likely to be generalisable to the wider population.

However, the trial entry criteria specified that patients be sufficiently fit to undergo local anaesthetic thoracoscopy under light sedation, which may make the results less applicable to those patients presenting with a greater degree of frailty. Furthermore, the trial was conducted on an open-label basis, which may have influenced the results of patient-reported measures, such as pain or breathlessness. It is also probable that those clinicians responsible for the recruitment and trial interventions were also required to assess patients for pleurodesis failure, introducing the potential for bias (although this was considered and addressed through blinded re-assessment).

Overall, the TAPPS trial has robustly demonstrated that there is no additional benefit in performing talc poudrage at local anaesthetic thoracoscopy over bedside chest drain and talc slurry for the management of malignant pleural effusion.

Trial registration

This trial is registered as ISRCTN47845793.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Scientific background

Pathophysiology of malignant pleural effusion

In a healthy individual, only a potential space exists between the two pleural layers (visceral and parietal). A small volume of fluid is continuously produced and absorbed in equal measure. Absorption occurs via a series of channels and pores, which are concentrated in the dependent portions of the parietal pleura.[1]

Malignancy can affect the pleura in a number of ways, all of which are likely to contribute to the formation of malignant pleural effusion (MPE) through the disruption of the normal cycle of fluid production and resorption. Direct tumour effects, typically as a result of primary tumour formation (mesothelioma) or metastatic deposition, can lead to physical obstruction of drainage outlets. Indirect effects are thought to arise as a result of cytokines, for example vascular endothelial growth factor, that either are secreted locally or exert their influence via the bloodstream. Indirect effects are thought to arise as a result of cytokines, for example vascular endothelial growth factor, which either are secreted locally or exert their influence via the bloodstream, resulting in increased vascular permeability and/or pleural neoangiogenesis, both of which predispose an individual to pleural fluid formation.[2–4] The end result of these processes is a net increase in the volume of fluid in the pleural space, resulting in an effusion that may, in certain cases, lead to physical restriction and the development of associated symptoms.[5] A particular hallmark of MPE is the tendency to recur or to progress despite treatment or drainage.

Burden of malignant pleural effusion

Autopsy series have suggested that as many as 15% of cancers will lead to some form of macroscopically evident pleural invasion.[6] Despite this, it is probable that the incidence of MPE is under-reported, as detection of malignant cells in fluid may be challenging[7] and not all patients develop symptoms.

Data suggest that there are around 40,000 new cases of MPE in the UK each year,[8] although these figures may well prove to be conservative as improved detection techniques and life-prolonging treatments become increasingly available. In addition, projections would estimate that there will be a year-on-year rise in the number of newly diagnosed malignancies over the coming decade, driven largely by increases in population.[9]

Survival in malignant pleural effusion

Malignant pleural effusion is usually a result of a metastatic process; therefore, patient survival is typically poor. In general, average survival is quoted as being 4–6 months from diagnosis, although these data are drawn from highly heterogeneous patient groups.[10–12] In addition, there are a number of factors that appear to influence survival, meaning that this figure may be less applicable to a number of patients. The underlying cancer type, in particular, appears to exert a strong influence on outcome, with some series reporting that those patients with mesothelioma (12 months) or breast cancer (> 2 years) survived longer.[11,13]

General approaches to malignant pleural effusion management

For many patients, MPE can lead to debilitating symptoms, such as breathlessness or chest pain.[5] General management of both of these symptoms, and others that may be associated with the underlying cancer, form the cornerstone of all treatment strategies; however,[14] in those patients with clinically significant volumes of fluid, drainage is usually indicated in addition to broader symptomatic management. Therapeutic aspiration of pleural fluid, whereby fluid is drawn off using simple apparatus, such as a needle and syringe, can lead to rapid relief for many patients and is readily performed in the outpatient setting, although the volumes that can be removed in a single sitting are limited by the potential adverse effects of rapid, high-volume

lung re-expansion.[15] For this reason, thoracocentesis is usually considered to be a temporising measure rather than a definitive treatment, with recurrent aspirations reserved for those patients with a very short life expectancy.[5]

Broadly, definitive MPE treatment can be divided into two approaches: (1) long-term fluid management and (2) attempted fluid prevention. The fluid management approach accepts that fluid will recur and prioritises treatments that will minimise patient time spent in hospital; in the UK, this typically involves the insertion of an indwelling pleural catheter (IPC). IPCs are inserted as a day-case procedure under local anaesthetic and are then drained regularly in the community by nursing teams, family members or the patient themselves. Despite their potential benefits, an IPC cannot be relied on to stop fluid forming. Recent data suggest that this occurs in approximately 20% of cases when drained at a typical frequency.[16,17] In addition, for some, the inconvenience of a permanently sited tube, and the regular drainages it demands, preclude IPC use.[18] Furthermore, treatment with an IPC requires the infrastructure to insert and manage the devices alongside the financial capability to support the regular use of the consumables they require, factors that prevent their use in several countries.

The more traditional and established approach to MPE treatment is fluid prevention, or pleurodesis. An attempt at pleurodesis begins with emptying the chest of as much fluid as possible, which is usually accomplished following insertion of an intercostal chest drain (at the bedside under local anaesthetic) or during a thoracoscopic procedure (which may be performed under either light sedation or general anaesthesia). Once the pleural cavity is evacuated, an irritant is applied to the pleural linings with the intention of stimulating a local inflammatory response, resulting in fibrosis and adhesion, effectively obliterating the pleural space and, hopefully, preventing any further effusion formation. The primary perceived benefit of the pleurodesis approach is that a single intervention period can lead to long-term fluid prevention. A number of small series have described success rates in excess of 80%.[5] However, as with the alternative, a degree of compromise is necessary as pleurodesis approaches usually require a period of inpatient treatment and may lead to more pain.[19,20]

In terms of patients' symptoms, recent randomised controlled trial (RCT) evidence suggest that there is parity between the pleurodesis approach and the fluid management approach with an IPC, with both interventions improving symptoms to a clinically meaningful degree.[20] Many centres, therefore, will choose to offer patients the choice of how they wish their recurrent fluid to be managed: as an outpatient with an IPC or as an inpatient with an attempt at pleurodesis.

Selecting a pleurodesis agent

In 2016, a Cochrane network meta-analysis[21] examining the efficacy of various treatments for the management of MPE was published. This study identified 62 RCTs for inclusion and used pleurodesis failure rate as its primary outcome measure, but noted that there was an extremely high degree of heterogeneity in the design and outcome reporting of the included studies, with a high risk of bias in many of them. With these limitations, the conclusion was that talc is likely to be the most efficacious agent, overall, for inducing pleurodesis and, in particular, it was suggested that talc given in the form of poudrage (sprayed directly onto the pleural as a dry powder during a thoracoscopic procedure) was the best approach.[21] It was recommended, however, that a more effective comparison between this method and the alternative delivery method for talc – as a slurry following drainage via bedside chest tube – be undertaken in the future.[21]

Talc slurry via chest tube is the current standard treatment approach for pleurodesis in the UK.[5] This method has become ubiquitous, as it is easily undertaken in the ward setting, with chest drain insertion possible at the bedside and not typically requiring anything other than local anaesthesia. Talc poudrage requires the capability to perform a thoracoscopy and for the patient to be able to tolerate such a procedure. Thoracoscopy may be undertaken by surgeons under general anaesthetic [video-assisted thoracoscopic surgery (VATS)] or, as is increasingly the case in the UK, under light sedation [local anaesthetic thoracoscopy (LAT)], the latter usually being performed by respiratory physicians in a dedicated procedural environment.[22]

Current evidence comparing the use of talc poudrage with slurry

Previous randomised controlled trials

Three studies have directly compared talc slurry with talc poudrage in a randomised setting, totalling 599 patients, and describe conflicting results.[23–25] All of these studies delivered poudrage using VATS under general anaesthesia; to the best of our knowledge, there are no studies that have examined talc poudrage delivered at LAT.

The earliest of these, Yim *et al.*,[23] which included 57 patients from a single centre, concluded that there was no significant difference between the two treatments and thus, because of the likelihood of increased resources being required, recommended that talc slurry be the treatment of choice. This study, however, as well as being significantly underpowered, chose to exclude all patients who were taking anticancer therapies, which makes the study population less applicable to the typical patient presenting with MPE.[23]

In 2009, Terra *et al.*[24] randomised 60 patients from a single centre, with the primary intention of examining post-pleurodesis lung expansion. Although this was found to be better in the poudrage arm, this did not translate into a meaningful clinical difference over longer-term follow-up. Once again, however, the wider applicability of this study's results may be questioned, as the population had an unusually low average age (55 years) and the majority of patients were female, a trait also shared by the earlier Yim *et al.*[23] study.

To the best of our knowledge, the largest study addressing the question of talc delivery for pleurodesis was performed by Dresler *et al.*,[25] reported in 2005. Participants were drawn from multiple North American centres over a 5-year recruitment period and had to meet entry criteria that included being suitable for general anaesthetic, having a performance status score of 0–2 and having an expected survival of ≥ 2 months. Participants were excluded if they had received any previous intrapleural therapy, if they had recently received systemic anticancer treatment or if they had bilateral effusions. Following randomisation, patients would proceed on protocol only if there was evidence of adequate lung expansion. Patients in the slurry arm had a chest tube (of unspecified size) inserted prior to 4–5 g of ungraded talc being instilled. Those patients undergoing poudrage received the same dose of talc if the operating surgeon was satisfied with a visual assessment of lung expansion, followed by drain insertion.[25]

The primary outcome for the Dresler *et al.* study[25] was successful pleurodesis at 30 days. Secondary outcomes included patient-reported breathlessness using a visual analogue scale (VAS), patient satisfaction, complications, time to recurrence and quality of life using the Quality of Life Questionnaire – Cancer 30 (QLQ-C30). Interpretation of the primary end point was based on the reviewing surgeon's interpretation of the chest radiograph, although the authors state that a radiological opinion was also sought to corroborate this.[25]

After withdrawals and exclusions, a total of 482 patients (slurry, $n = 240$; poudrage, $n = 242$) were included in the final analysis. Based on intention to treat, no significant difference was found between the two arms at 30 days. Following a per-protocol analysis, whereby trapped-lung patients were excluded, a significant difference ($p = 0.045$) was found, favouring poudrage, although this effect disappeared when only patients who were alive at 30 days (slurry, $n = 130$; poudrage, $n = 152$) were included. Of note, a high number of complications were reported, including a perioperative mortality rate of 8.4% and a respiratory failure rate of 8.1% in the poudrage arm. A post hoc analysis suggested that poudrage might be more effective in those patients with MPE due to breast and lung malignancies.[25]

Although undoubtedly important, the Dresler *et al.* study[25] has not defined practice as it was felt to have encompassed several potentially important flaws and barriers to wider generalisability, particularly in the UK. With the benefit of hindsight, these included a lack of detail regarding how randomisation, concealment or powering of the trial occurred; the use of ungraded talc; the use of VATS and general anaesthetic; the lack of an economic evaluation to inform broader utility and cost-effectiveness; poor retention to follow-up; major differences in treatment arms, such as assessing trapped lung using radiology

in the slurry arm and intraoperatively in the other; no attempt at stratification prior to randomisation; the use of post hoc analyses to draw and report study conclusions; and, perhaps most importantly, a lack of what may be seen to be a clinically relevant or patient-centred definition of pleurodesis success.[25,26]

Health economic analyses comparing slurry with poudrage

No published studies have directly measured the costs or cost-effectiveness of talc poudrage compared with talc slurry for MPE; the limited number of studies in this area have tended to focus on the comparative costs of IPC use following their introduction approximately 15 years ago.[27–29] Two of these studies,[27,29] however, used theoretical modelling to compare treatments and included slurry and poudrage in their analyses. The first,[27] published as a 2011 conference abstract, is the only study to include LAT-delivered poudrage as well as VATS poudrage, suggesting both that the latter was dramatically less cost-effective than the former and that LAT poudrage and that talc slurry were very similar in terms of cost-effectiveness.[27] The second study, a further modelling exercise by Puri *et al.*,[29] suggested that talc slurry is the optimal approach for patients with a life expectancy of $\geq$ 1 year, when compared with either IPC or thoracoscopic poudrage (the authors do not specify LAT or VATS).[29]

Local anaesthetic thoracoscopy in the UK

In the UK, over the last 20 years, there has been an expansion in the number of centres able to offer physician-delivered LAT services.[22] The wider availability of LAT services, and, by extension, of talc poudrage, potentially opens up the possibility of treatment of MPE to a broader geographical range of patients than VATS allows, as well as opening up the possibility of treatment to those patients who would perhaps be unsuitable for general anaesthesia. It should be noted, however, that LAT is currently used primarily as a diagnostic tool, with the overwhelming majority of procedures being performed in patients with a suspected, but not yet established, diagnosis of pleural malignancy. In such a scenario, talc poudrage may still be performed prior to conclusion of the procedure in order to reduce the likelihood of a patient needing a further intervention for MPE later in their disease course.

Rationale for research

How best to deliver talc into the pleural space remains an unanswered but important question, with the relatively poor-quality data described in *Current evidence comparing the use of talc poudrage with slurry* failing to provide robust evidence to drive standardised clinical practice. This is particularly the case in the UK, where the pleurodesis approach offered will often be based on the individual preferences or beliefs of the treating clinician and the locally available facilities. Advocates for thoracoscopy and poudrage suggest that this procedure, despite being more involved for patients and requiring greater health-care infrastructure, offers a higher chance of long-term pleurodesis success (due to a more even powder distribution) and a shorter initial stay in hospital (as all fluid is drained immediately prior to poudrage, rather than waiting for it to drain gradually). Opponents to poudrage argue that there is a lack of evidence to support the view that poudrage is better than slurry, and that the probable excess costs, lower availability and requirement for greater baseline patient fitness make it the less preferable approach in routine care.

Primary research aim

The evaluating the efficacy of Thoracoscopy And talc Poudrage versus Pleurodesis using talc Slurry (TAPPS) trial aimed to be the first adequately powered, robustly designed trial to compare the efficacy of talc poudrage (administered using LAT) with the current standard treatment of a chest drain followed by talc slurry, for the management of patients with MPE in the UK.

Research questions

The primary research question was, 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 the standard therapy of chest drain insertion and talc slurry instillation?

The secondary research questions were as follows:

- Does talc poudrage reduce the time to pleurodesis failure at 1 and 6 months post randomisation when compared with talc slurry?
- Does talc poudrage at thoracoscopy improve chest radiographic appearances after initial drain removal and at 1, 3 and 6 months post randomisation when compared with talc slurry?
- Does talc poudrage cause less breathlessness and thoracic pain for the first 7 days post randomisation when compared with talc slurry?
- Does talc poudrage improve health-related quality of life (HRQoL) over the 6 months post randomisation when compared with talc slurry?
- Does talc poudrage reduce health-care utilisation during the 6 months post randomisation when compared with talc slurry instillation?
- Is talc poudrage cost-effective over 6 months when compared with talc slurry instillation?

Chapter 2 Main trial design and methods

Trial design

The trial was a pragmatic, multicentre, UK-based, open-label RCT comparing two methods for delivering talc for the management of MPE: (1) bedside chest drain and talc slurry and (2) LAT and talc poudrage. The trial was not registered as a Clinical Trial of an Investigational Medicinal Product following discussion with the Medicines and Healthcare products Regulatory Agency. A within-trial economic evaluation was conducted to assess the cost-effectiveness of both approaches.

The trial protocol has been published and is available on an open-access basis.[26] A general summary of the trial processes can be found in *Figure 1*.

Table 1 describes the main differences between the TAPPS trial and the 2005 Dresler *et al.* study.[25]

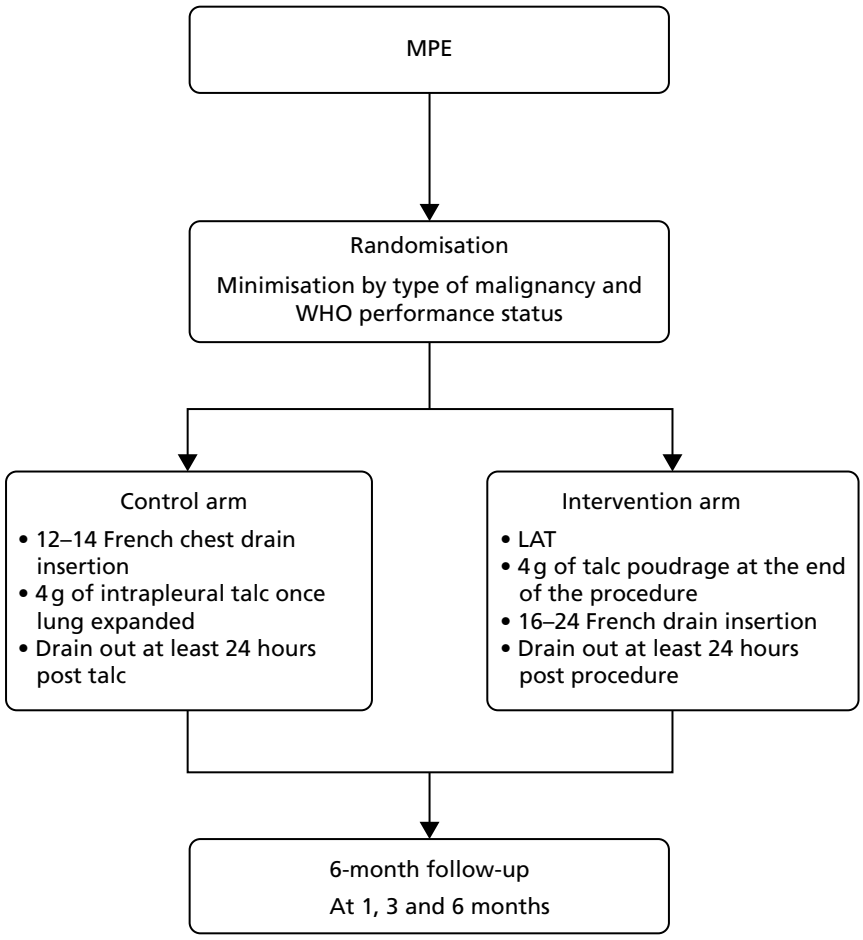

FIGURE 1 Trial summary flow chart. WHO, World Health Organization.

TABLE 1 Major differences between the TAPPS trial and Dresler *et al.* study[25]

Dresler *et al.*[25]	TAPPS trial
VATS only	Medical LAT
Radiological outcome	Clinical definition of pleurodesis
No health economics	Full health economics
1-month primary end point	3-month primary end point
No stratification	Minimisation
Disparity between pleurodesis methods	Standardisation of therapy as best as possible
Ungraded talc	Graded talc
Post hoc subgroup analysis	A priori subgroup analysis

Ethics approval

The TAPPS trial was given initial ethics approval by the National Research Ethics Service Committee (North West – Preston) on 26 June 2012. The ethics approval number was 12/NW/0467.

All subsequent substantial amendments were reviewed and approved by the same committee.

Trial registration

The TAPPS trial was prospectively registered on the publicly accessible International Standard Randomised Controlled Trial Number (ISRCTN) database prior to recruitment beginning (ISRCTN47845793).[30] A comprehensive lay summary was also prepared and made available on the Cancer Research UK website.[31]

Trial oversight and management

The trial was sponsored by North Bristol NHS Trust (local identification number 2843).

The TAPPS trial was managed jointly by research teams based at the University of Bristol and the University of Oxford. The chief investigator, trial co-ordinator and lead trial nurse were based at the Academic Respiratory Unit at the University of Bristol. The trial manager, trial database and data entry team were based at Oxford Respiratory Trials Unit at the University of Oxford.

A Trial Management Group met and communicated regularly to ensure efficient day-to-day running of the trial, protocol adherence, and that adverse events (AEs) and safeguarding issues were identified and acted on swiftly.

The Trial Steering Committee (TSC) met at regular intervals (at least twice per year) and, in addition to the chief investigator and trial statistician, consisted of independent physician and lay members in accordance with the funder's requirements.

An Independent Data and Safety Monitoring Committee met at regular intervals during the trial. After reviewing the necessary data, they provided a recommendation to the chairperson of the TSC with regards to trial continuation.

Participant selection and trial recruitment centres

Inclusion criteria

- Clinically confident diagnosis of MPE requiring pleurodesis, defined as:
  - pleural effusion with histocytologically proven pleural malignancy, or
  - pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid, or
  - pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging without a clear alternative cause for fluid.
- Fit enough to undergo LAT.
- Expected survival of > 3 months.
- Written, informed consent to trial participation.

Exclusion criteria

- Patients in whom thoracoscopy is the only reasonable approach to making a diagnosis and in whom such a diagnosis would significantly influence further management.
- Aged < 18 years.
- Female patients who were pregnant or lactating.
- Evidence of extensive lung entrapment on chest X-ray (CXR) or computed tomography, or significant fluid loculation on ultrasound, to a level that would normally be a contraindication to attempted talc pleurodesis.
- Insufficient volume or position of pleural fluid on lateral decubitus thoracic ultrasound to safely perform LAT without further intervention being necessary.
- Previously documented adverse reaction to talc.
- Clear contraindication to thoracoscopy or chest tube insertion.

Recruitment centre selection

To be considered for participation in the TAPPS trial, all recruitment centres needed to:

- have a local principal investigator (PI) with an interest in pleural disease
- have an established medical thoracoscopy service
- expect to see at least 20 potentially eligible patients per year.

[The original ethics submission included eight sites based in England. Subsequently, an additional nine sites (including centres in Wales and Scotland) were added. All site additions and removals were considered and approved by the TSC.]

Changes to the original trial protocol

All changes to the trial protocol were made following consideration and approval by the TSC and, when necessary, the Independent Data Monitoring Committee and ethics committee. Changes were typically made in response to poorer-than-expected recruitment rates and these are summarised in *Table 2*.

TABLE 2 Changes to the original trial protocol over the recruitment period

Study amendment number	Details of significant alterations to protocol	Resulting protocol version and date
1	Clarified various sections in the protocol	2.0; 1 December 2012
	Altered the time window for a patient to consider trial entry	
	Updated flow charts	
	Clarified the use of suction and telephone follow-ups	
2	No alterations as part of this amendment	
3	Adjustments to the follow-up visit windows	3.0; 14 August 2013
	Administrative details were updated throughout the protocol	
4	Change of time allowance between the randomisation and the trial procedure from 24 to 72 hours	4.0; 26 September 2013
	Minor administration changes and clarifications to the protocol	
5	No alterations as part of this amendment	
6	Edited the safety reporting section of the protocol	5.0; 1 June 2014
	Updated administrative details throughout the protocol	
	Added protocol appendix 6	
7	Updated secondary end points following ratification of SAP version 1.0	6.0; 6 October 2014
	Updated trial end date	
	Updated trial recruitment centre and PI details	
	Minor clarifications	
8	Clarified that the first 7 days of VAS measurements were to be taken post procedure, not post randomisation	7.0; 5 December 2014
	Removed Leicester as recruiting site	
9	Updated the PI at Wythenshawe Hospital	8.0; 2 October 2015
	Added information regarding new sites	
	Updated the change in TSC membership information	
10	Updated the PI at Addenbrooke's Hospital	9.0; 5 October 2016
	Removed Birmingham and Wrexham as active recruiting sites	
	Updated trial recruitment end date	

SAP, statistical analysis plan.

Sample size

The sample size calculation and all statistical analyses were performed using Stata® v15.1 (StataCorp LP, College Station, TX, USA). Previous literature and local audit data suggested that patients with a European Cooperative Oncology Group (ECOG) 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.[5,25]

Therefore, 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, a total of 325 patients would be required.

The final recruitment target was rounded up to 330 patients, with 165 patients to be allocated equally to each treatment arm.

No interim analyses were planned.

Participant recruitment

Patient identification and screening

Potential participants were identified locally from a range of sources, including:

- discussions at local multidisciplinary team meetings
- routine outpatient appointments
- inpatient ward reviews
- referrals from colleagues in oncology or acute medical settings.

Patients were assessed against the inclusion and exclusion criteria on a consecutive basis. A patient information sheet was provided at the earliest opportunity, with each individual given enough time (in their own opinion) to consider trial entry.

Each site maintained a local screening log. These were sent to the trial management team on a regular basis and were used to identify potential challenges to recruitment and/or general patterns of behaviour among patients and clinicians.

Informed consent

All participants provided written, informed consent to trial participation. It was suggested that consent be taken as close as possible to the proposed date of randomisation, but these could occur up to 7 days apart when necessary. A separate consent form was signed if the patient was willing to agree to sample collection and storage for possible genetic testing in the future.

In addition to the above, all sites were expected to obtain separate consent for whichever procedure the patient was allocated to, as per standard NHS practice.

Randomisation, concealment and blinding

Following consent, patients were randomly assigned, in a 1 : 1 ratio, to one of the treatment allocations detailed below (see *Treatment groups*). Randomisation was performed centrally by the Trial Management Team in Oxford. The team accessed an external computer-based system (Sealed Envelope™, London, UK) on behalf of the randomising site, with local investigators required to confirm eligibility verbally over the telephone before being notified of the allocation. Strict allocation concealment was maintained, with treatment allocations becoming available only after the participant was enrolled and entered into the randomisation system.

Minimisation with a random component of 80% was utilised. The minimisation factors were:

- type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other)
- World Health Organization (WHO)/ECOG performance status (0 or 1, 2 or 3).

It was intended that randomisation occur as close as possible to the intended procedure time.

Because of the inherent and substantial differences between the two methods being tested, this trial could not be performed ethically or safely in a blinded manner using dummy or sham procedures. The trial was undertaken in an open-label manner, such that both the trial participant and the research team were aware of the allocated intervention; however, the trial management team, including the TSC and Trial Management Group, were blind to patient-level data throughout.

Treatment groups

A summary of the treatments given in each group can be found in *Figures 2* and *3*.

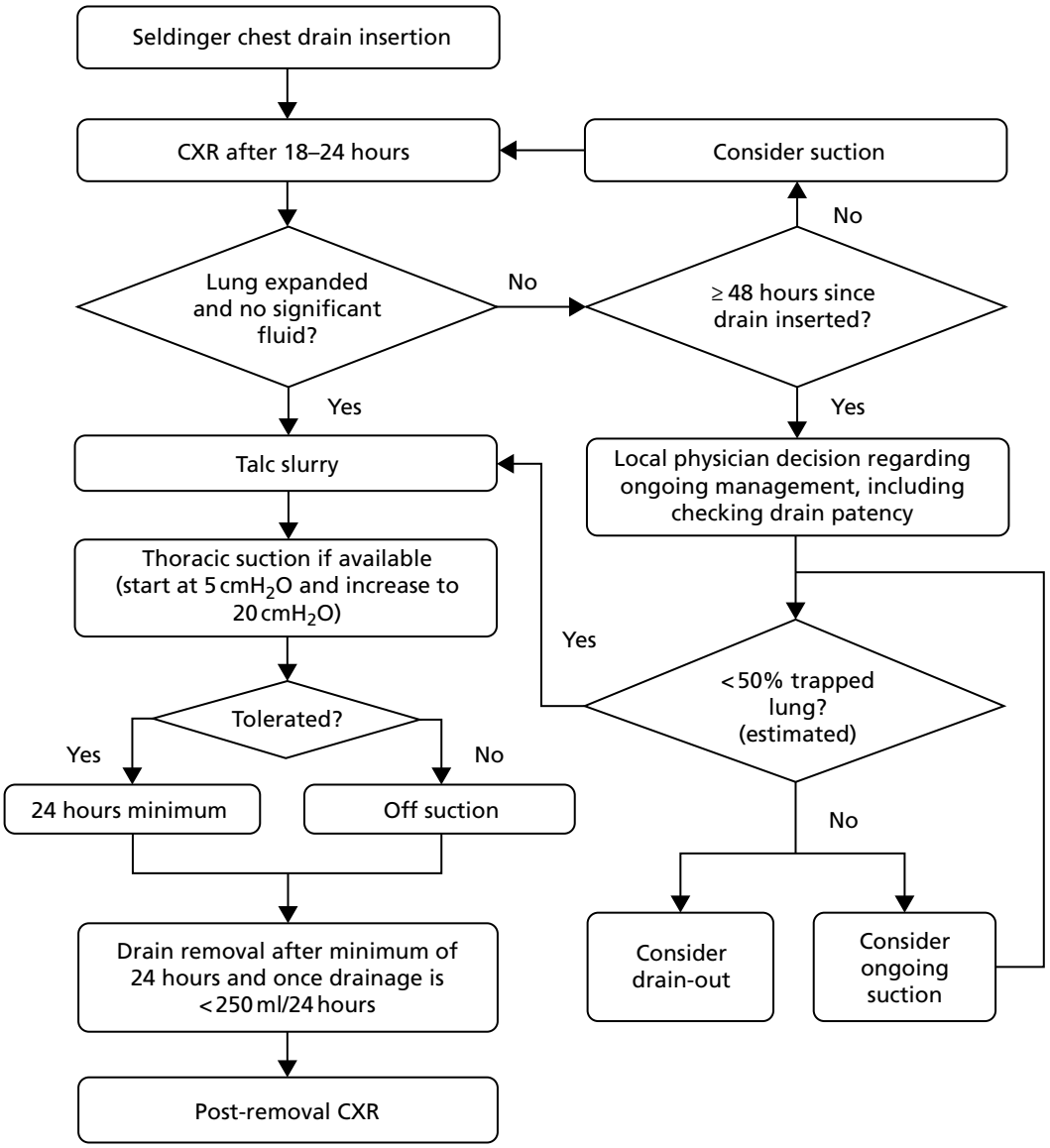

FIGURE 2 Summary of treatments in control (slurry) arm.

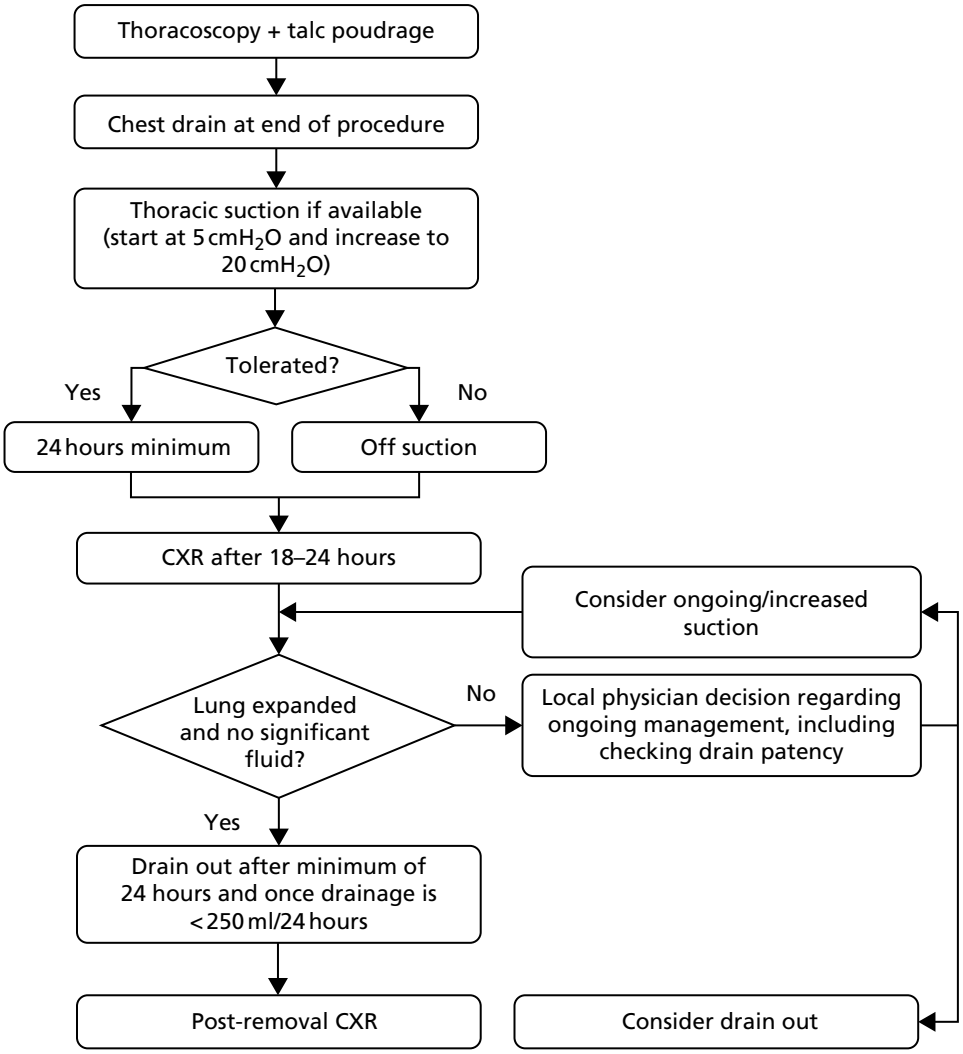

FIGURE 3 Summary of treatments in intervention (poudrage) arm.

Control (slurry) group

Post randomisation, patients allocated to the control group underwent the following:

- Admission to an appropriate clinical area.
- Contemporaneous thoracic ultrasonography to guide drain placement.
- Pre-medication with analgesia as required.
- Instillation of local anaesthesia to proposed drain site.
- 12–14 French gauge chest drain insertion, using Seldinger technique, by an individual of adequate training and experience.
- Assessment with CXR between 18 and 24 hours post drain insertion.
- Those patients without significant ongoing pleural opacification and/or unexpanded lung were given 4 g of sterile talc slurry (see *Appendix 1* for full procedure). Those patients with ongoing opacification or unexpanded lung could be placed onto thoracic suction at the discretion of the treating physician. When on suction, patients underwent CXR every 24 hours with local teams instructed to consider talc slurry instillation when there was evidence of at least 50% pleural apposition (by visual estimation).
- Thoracic suction (if available and tolerated) for a minimum of 24 hours post talc instillation.
- Drain removal, CXR and consideration for discharge once < 250 ml of fluid output was recorded in a 24-hour period.

Intervention (poudrage) group

Post randomisation, patients allocated to the intervention group underwent the following:

- Admission to an appropriate clinical area and listing for LAT at the earliest opportunity.
- LAT as per local standard practice (to include ultrasound guidance and light sedation), with complete fluid drainage and diagnostic pleural sampling as required, performed by an individual of appropriate training and experience.
- Talc poudrage with 4 g of sterile talc slurry (see *Appendix 1* for full procedure).
- Insertion of a 16–24 French gauge chest drain at the end of the procedure.
- Thoracic suction (if available and tolerated) for a minimum of 24 hours immediately after the procedure.
- Assessment with CXR between 18 and 24 hours post procedure (with ongoing use of suction if deemed to be necessary).
- After a minimum of 24 hours, drain removal, CXR and consideration for discharge once < 250 ml of fluid output was recorded in a 24-hour period.

Standard care and co-enrolment during the trial period

During the trial, for all issues other than those pertaining to the drainage and management of the MPE, treatment discretion lay with the primary clinician.

Normal clinical review during the trial period was to take place in the usual outpatient or inpatient setting. The frequency of clinical review depended on patient choice, severity of symptoms and clinical discretion.

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

An individual patient could be enrolled into the TAPPS trial only once. Once entered, patients were not to be enrolled in any other trial that looked to directly influence the production of pleural fluid until the end of their trial participation. Patients could still be considered for other studies, such as chemotherapy trials, but discussion was to take place prior to enrolment to ensure compatibility between protocols.

Trial assessments and timings

Baseline assessment

Participants underwent a baseline assessment prior to their trial procedure. The standardised assessment was to include:

- relevant current and past medical history
- symptom scores for pain and dyspnoea
- recent blood results
- quality-of-life assessments.

Intervention and inpatient period

Standardised data collection regarding the trial intervention was obtained, along with details of AEs in the early post-procedure period.

Documentation of inpatient trial activity and outcomes was recorded in a standardised fashion at the time of discharge.

Follow-up period and assessment of increasing breathlessness

Trial follow-up appointments took place at:

- 1 month (day 28 ± 7 days)
- 3 months (day 84 ± 10 days)
- 6 months (day 168 ± 14 days) post randomisation.

These appointments took place in the patient's local trial hospital or an appropriate satellite centre, and consisted of a standardised assessment and CXR.

All patients who were felt to have increasing breathlessness during the follow-up period were recommended to undergo CXR. Any CXR that showed a degree of pleural opacification ipsilateral to the pleurodesis attempt led to further imaging to confirm the presence of fluid. If fluid was confirmed and the CXR showed pleural opacification to be one-third or greater than the volume of the hemithorax (by visual estimation), the primary physician could undertake any further investigations or interventions as deemed appropriate.

In patients who had less than one-third of the hemithorax occupied by pleural fluid, the primary physician was to discuss with another local physician, who was blinded to treatment arm, whether or not pleural intervention was required. In the event of disagreement, or being unable to find a blinded physician, the chief investigator could be contacted to make a casting decision (without being informed of the treatment arm).

Patient-reported outcomes

Trial participants were asked to complete two forms of patient-reported outcome measure:

1. VAS score for chest pain and dyspnoea
   VAS scores were recorded at baseline and then daily for the first 7 days post procedure; following this, scores were recorded on a weekly basis and at each follow-up visit
2. quality-of-life questionnaires
   the EuroQol-5 Dimensions, five-level version (EQ-5D-5L), and Short Form questionnaire-36 items (SF-36) HRQoL questionnaires were completed by all participants at baseline and at each subsequent trial visit.

Health economic diaries

Patients were provided with pre-printed diaries to keep with them for the duration of their trial involvement. They were asked to record details of all personal contact with medical professionals (excluding trial visits) in a basic standardised manner. These data were reviewed at each follow-up appointment.

An example of a standardised diary may be found in *Report Supplementary Material 1*.

Data acquisition and management

Data were collected in a variety of ways, depending on the type of information being acquired. All information from trial visits was recorded locally on a series of paper case report forms, which were copied and sent to the trial data team for screening, transcription and entry into the main database, which was run using the OpenClinica 3.12.2 platform (OpenClinica LLC, Waltham, MA, USA).

The case report forms were supplemented by VAS collection booklets (see *Report Supplementary Material 2*) and health-care utilisation diaries, as described above, which patients completed at home and brought to each trial visit.

Outcome measures

Primary outcome

The primary end point was the number of patients who experienced pleurodesis failure up to 3 months (90 days) post randomisation.

A patient was defined as experiencing pleurodesis failure if they underwent any of the following procedures on the side ipsilateral to their trial intervention:

- therapeutic pleural aspiration of ≥ 100 ml
- insertion of an intercostal drain for fluid drainage
- insertion of an IPC
- medical or surgical thoracoscopy.

A patient was also deemed to have failed pleurodesis if their primary physician decided that they required one of the above pleural interventions, but the intervention was not performed (e.g. in the event of death or patient choice against procedure).

The 90-day end point was chosen with a view to providing useful clinical information to patients with a presumed average life expectancy of 4–6 months, as was expected in the target trial population. Although failure rate at 30 days had previously been used in a major study,[25] this was felt, in general, to be too short an interval. Conversely, we believed a primary outcome measured later, at 180 days post randomisation, would increase the risk of insufficient data being available due to mortality from underlying malignancy. Nonetheless, pleurodesis failure at both 30 and 180 days were included as secondary outcomes.

Secondary outcomes

In addition to the above, the following secondary outcomes were assessed:

- the number of patients with pleurodesis failure up to 30 days post randomisation
- the number of patients with pleurodesis failure up to 180 days post randomisation
- percentage radiographic (CXR) pleural opacification at the 1-, 3- and 6-month post-randomisation follow-up visits, and after initial drain removal
- self-reported HRQoL at the 1-, 3- and 6-month follow-up post-randomisation visits, as measured using the SF-36 and EQ-5D-5L questionnaires
- self-reported thoracic pain and breathlessness at 7 days post procedure, and at 30, 90 and 180 days post randomisation, measured using VAS scores
- all-cause mortality up to 180 days post randomisation
- time to pleurodesis failure, censored at 180 days post randomisation
- number of nights spent as a hospital inpatient up to 90 days post randomisation, including length of initial stay.

The original trial protocol also included the following secondary outcome: requirement for further pleural procedures up to 180 days post randomisation, based on an independent, blinded assessment. However, following approval from the TSC, this outcome was removed prior to the trial database being locked. The reason and justification for this change can be found in *Table 3*.

TABLE 3 Summary of changes to the original statistical analysis plan

Change	Notes/justification
Changed method of analysis for pleurodesis failure from competing risk time-to-event model to logistic regression model	To match what was specified in the protocol
Removed secondary outcome 'requirement for further pleural procedures up to 180 days post randomisation, based on an independent, blinded assessment'	Blinded assessment and corroboration of the need for pleural intervention were already required for any case, which is likely to be contentious. Without clinical contact, the information on which specified assessment would be made was felt to be insufficient to determine whether or not a further pleural procedure would have been necessary; thus, the clinical relevance of the outcome was felt to be doubtful. It is probable that this assessment would have relied primarily on the patient's CXR appearance, which is being addressed as another secondary outcome
Restricted subgroup analyses to only the primary outcome	
Updated Stata command for analysing CXR pleural opacification, EQ-5D-5L, SF-36, thoracic pain and breathlessness, from 'xtmixed'to 'mixed'	The command 'mixed' replaced 'xtmixed' in more recent versions of Stata
Removed sensitivity analysis for primary outcome based on measuring pleurodesis failure from date of procedure rather than date of randomisation	
Removed the subgroup analysis for use of NSAIDs at baseline	This question has now been addressed more comprehensively in the TIME1 trial
Removed the subgroup analysis for previous radiotherapy at baseline	This was not felt likely to be of clinical relevance
Added additional exploratory outcomes	
Specified that AEs and SAEs would be summarised and analysed within 7 days of randomisation (in addition to within 30 and 180 days)	To better reflect the immediate post-procedure and inpatient period

NSAID, non-steroidal anti-inflammatory drug; SAE, serious adverse event; TIME1, the first Therapeutic Interventions in Malignant Effusion.

Exploratory outcomes

The following outcomes were added during the trial on a purely exploratory basis:

- categorical version of percentage radiographic (CXR) pleural opacification at the 1-, 3- and 6-month post-randomisation follow-up visits and after initial drain removal, with categories –
  - no fluid visible
  - 1–24% opacification due to fluid (small effusion)
  - 25–49% due opacification due to fluid (moderate effusion)
  - ≥ 50% opacification due to fluid (large effusion)
- degree of visible lung entrapment on CXR at 6 months post randomisation, with categories –
  - no lung entrapment
  - minor lung entrapment (1–24% unexpanded lung)
  - moderate lung entrapment (25–49% unexpanded lung)
  - severe lung entrapment (≥ 50% unexpanded lung).

These additions occurred without the Trial Management Team being aware of any results, following completion of recruitment but before database lock.

Adverse events

Adverse events and serious adverse events (SAEs) were defined, documented and assessed in line with standard practice. All SAEs were independently reviewed with regards to safety (by the sponsor) as close as possible to the time of occurrence. On completion of the trial, all AEs and SAEs were independently reviewed and coded.

Statistical analysis

The primary analysis for each outcome was performed using intention-to-treat principles, meaning that all patients on whom an outcome was available were included in the analysis, and were analysed according to the treatment group to which they were randomised.[32] Patients with missing outcome data were excluded from the analysis. All tests were two sided and were considered statistically significant at the 5% level.

All analyses were adjusted for the minimisation variables, with these included as covariates in the regression model for each outcome[33,34] [type of underlying malignant disease (mesothelioma, lung cancer, breast cancer, other) and WHO performance status (0–1 or 2–3)].

Primary outcome

The primary outcome (pleurodesis failure at 90 days post randomisation) was analysed using a logistic regression model. As specified above, the model was adjusted for the minimisation variables and excluded patients with missing outcome data.

Subgroup analyses

Subgroup analyses were prespecified and performed for the primary outcome. Results from subgroup analyses were viewed as hypothesis-generating only. The following analyses were performed:

- patients receiving anticancer therapy at baseline compared with those patients not receiving anticancer therapy at baseline
- WHO performance status (0 vs. 1 vs. 2 vs. 3)
- patients on steroids at baseline compared with those patients not on steroids at baseline
- previous attempt at pleurodesis in the previous month compared with no attempt in the previous month
- patients with primary malignancy of breast cancer compared with mesothelioma, lung cancer and other cancer.

Secondary outcomes

- Pleurodesis failure at 30 and 180 days was analysed in the same manner as the primary outcome, using a logistic regression model adjusted for the minimisation factors.
- Percentage chest radiographic opacification was analysed using a mixed-effects linear regression model. Fixed effects were treatment group, time point, a treatment-by-time interaction and the minimisation factors. An unstructured correlation matrix was used to model the correlation between outcomes at different time points.
- HRQoL, using the EQ-5D-5L and SF-36 questionnaires, was analysed using the same approach as percentage chest radiographic opacification above (i.e. using mixed-effects linear regression model, adjusted for treatment, time point and a treatment-by-time interaction). In addition to the minimisation factors, the analyses also adjusted for baseline questionnaire scores.
- Chest pain and dyspnoea were analysed using the same approach as above and adjusted for the baseline VAS scores.
- All-cause mortality was analysed using a logistic regression model.
- The time to pleurodesis failure was analysed using a Fine–Gray competing risk time-to-event model, with mortality as the competing risk.[35]
- The number of days spent in hospital was analysed using a negative binomial regression model, with the number of days of follow-up included in the model as an offset.

Exploratory outcomes

- The exploratory outcome of the categorical version of percentage radiographic pleural opacification was analysed using a mixed-effects ordinal logistic regression model, with a random intercept for patient. The model was adjusted for the minimisation variables.
- The exploratory outcome of the degree of visible lung entrapment was analysed using an ordinal logistic regression model, adjusted for the minimisation variables.

Bias reduction

Because of the open-label nature of this trial, the potential for introducing bias into data collection and analysis was considered inherently greater than if the trial was performed in a fully blind fashion, especially given that the local trial research teams were typically also responsible for the clinical management of participants. 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 was discussed with a blinded assessor. This blinded assessor could be a clinician at the local recruiting site or, if necessary, the chief investigator.

Changes to original statistical analysis plan

All changes to the original statistical analysis plan were agreed by the TSC and occurred prior to the trial database being locked.

A summary of the changes can be found in *Table 3*.

Sensitivity analyses

Sensitivity to missing data for the primary outcome was assessed under a range of missing-not-at-random scenarios. For each scenario, a treatment effect and 95% confidence interval (CI) were calculated and compared with results from the main analysis of the primary outcome to see if conclusions were affected by different assumptions regarding the missing data.

Chapter 3 Health economic analysis design and methods

Objective

The objective of the health economic element to the trial was to determine whether or not a LAT-delivered talc poudrage was more cost-effective than standard chest tube talc slurry pleurodesis in patients with MPE.

Analysis perspective and aims

The health economic analysis took place from a UK NHS and Personal Social Services perspective. HRQoL data and health-care resource use and cost data were used to examine the following:

- the cost of performing both trial interventions
- the follow-up health-care resource use and costs for trial participants in both groups
- HRQoL, through calculation of utility values using the EQ-5D-5L and Short Form questionnaire-6 Dimensions (SF-6D)
- the incremental cost-effectiveness ratio (ICER) when thoracoscopy-delivered talc poudrage was compared with standard chest tube talc slurry pleurodesis.

Data collection

Quality of life

Generic HRQoL was measured using the SF-36 and the EQ-5D-5L.[36,37]

In the EQ-5D-5L, patients are asked to think about their health on the day that they are completing the questionnaire and to report any problems (none, slight, moderate, severe and unable/extreme) on five attributes (mobility, self-care, usual activities, pain/discomfort and anxiety/depression). Patients are then required to rate their health using a 100-point VAS (0 = worst health you can imagine to 100 = best health you can imagine). The EuroQoL-5 Dimensions (EQ-5D) is a standardised measure of health, providing a simple generic measure of health for clinical and economic appraisal.

In the SF-36, patients are asked to think about their health in terms of eight health concepts: (1) physical functioning (10 items); (2) social functioning (two items); (3) role limitations due to physical problems (four items); (4) role limitations due to emotional problems (three items); (5) mental health (five items); (6) energy/vitality (four items); (7) pain (two items); and (8) general health perceptions (five items). It also includes questions providing an indication of perceived change in health.

Both quality-of-life questionnaires were completed at randomisation and then at 1, 3 and 6 months post randomisation.

Resource use

As part of the NHS and Personal Social Services perspective adopted, we included the following health and hospice care resource-use categories over the 6-month follow-up:

- Resource use involved with trial procedures, including time in surgical theatre; health-care staff involved; surgical disposables (e.g. surgical gowns, gloves, drapes, syringes, sutures and drains); medication (including talc) and sedation; capital equipment (e.g. video stack use, warmer, thoracoscopes and light cables); and investigations (e.g. thoracic ultrasound and CXRs).

- Initial hospitalisation after trial intervention. For each hospitalisation, information was recorded on the date of admission and discharge, and the dates of transfers between different specialty wards.
- Follow-up hospital resource use, including outpatient visits; visits to accident and emergency (A&E); ambulance use; outpatient visits; and day cases and length of stay in hospital, including stays in an intensive treatment unit.
- Community care use, including visits to a general practitioner (at surgery, home or through the telephone); nurse (at surgery or at home); physiotherapist; occupational therapist; psychologist; and counsellor.
- Palliative and hospice care, including contacts with a palliative care nurse and number of nights spent as an inpatient in a hospice.

Resource use involved with trial procedures was obtained by observing a number of trial interventions at the trial site at the Churchill Hospital (NHS Oxford University Hospitals NHS Foundation Trust). Details about the initial hospitalisation were obtained through a staff questionnaire to be completed once the patient had been discharged.

All other follow-up resource use was collected using patient questionnaires administered at 1, 3 and 6 months. As an aide memoire, patients were also provided with a resource-use log designed for them to fill in every time they had a contact with the health-care system. In the questionnaires, we did not distinguish whether the contacts with the health-care service were through the NHS, Personal Social Services or private providers, and we assumed that all contacts were financed by the NHS or Personal Social Services, in a bid to keep the questionnaires as simple as possible. For missing values (e.g. patients who died halfway through follow-up), clinical staff completed some of the questions, including ambulance and A&E use, outpatient visits and hospitalisations, through review of patients hospital records.

Unit costs

Unit costs for the initial hospital admission were derived from NHS reference costs for the year 2013/14,[38] as they contained information on costs by medical specialty. Unit costs for consultations with general practitioners and nurses were obtained from the Personal Social Services Research Unit's *Unit Costs of Health and Social Care* publications for 2015 and 2017.[39,40]

For all other contacts, unit costs were derived from the NHS National Schedule of Reference Costs 2016 to 2017.[41] For outpatient visits, we used the weighted average of all consultant-led, non-admitted, face-to-face attendances, either first or follow-up. For physiotherapists, occupational therapists and psychologists, we also used the weighted average of all consultant-led, non-admission, face-to-face attendances for each of these three therapists. In the absence of specific unit costs for counsellors, we assumed that these would be the same as for a psychologist. For visits to A&E, we used the weighted average of all emergency medicine contacts, excluding dental care and patient dead on arrival. For ambulance transport to A&E, the unit cost of a call to the emergency services was included as well as that for ambulance transport.

Using the reasons for hospitalisation reported by patients in the resource-use questionnaires, we obtained diagnosis and procedure codes. These were then translated into a Healthcare Resource Group (HRG) using the HRG4+ 2016/17 Reference Costs Grouper (NHS Digital). Each HRG was then linked to a series of elective, non-elective and day-case reference costs obtained from the 2016/17 schedule of reference costs. All costs were updated to 2016/17 using the Hospital and Community Health Service index.[40]

Statistical analysis

Quality of life

At each follow-up, responses to each of the five questions in the EQ-5D-5L were presented. As recommended by the National Institute for Health and Care Excellence (NICE),[42] EQ-5D-5L responses were converted into

utilities using the validated mapping function to derive utility values for the EQ-5D-5L from the existing EuroQol-5 Dimensions, three-level version.[43]

For each follow-up, the score for each of the eight dimensions of the SF-36 were coded, summed and transformed on to a scale from 0 (worst possible health state) to 100 (best possible health state). We also estimated the two standardised summary scores of the SF-36: the physical component score and the mental health component score.[37] SF-36 responses were then converted into utilities using the SF-6D algorithm developed by Brazier *et al.*[44]

The SF-36 items scores, utility values (both for the EQ-5D-5L and SF-6D) and EQ-5D VAS scores at each follow-up are presented as mean [standard deviation (SD)]. Mean differences across the two treatment groups are presented alongside 95% CIs, with statistical significance assessed using two-sided *t*-tests.

Quality-adjusted life-years

Survival was estimated using the Kaplan–Meier survival function 6 months post randomisation. A quality-adjusted survival curve was generated by plotting, against time, the product of the mean utility of patients living at time *t* and the probability of surviving to time *t*, in order to create three periods (i.e. randomisation to 1-month follow-up, 1- to 3-month follow-up and 3- to 6-month follow-up). The area under this quality-adjusted survival curve then gave the mean quality-adjusted survival in each treatment group. Utility was assumed to change linearly between each follow-up, rather than changing at the mid-point between follow-ups or being maintained from one follow-up to another.

For each treatment group, results are reported as quality-adjusted life-years (QALYs) with 95% CIs calculated non-parametrically from 1000 bootstrap differences. Mean QALY differences between the two patient groups were also presented with 95% CIs, estimated using the 1000 bootstrap differences. Results are presented for the whole patient sample (i.e. when patients who withdrew from the analysis were treated as censored and missing utility estimates were assumed to be the same as the mean for that treatment group).

Resource use

Initial length of stay and all follow-up contacts, at each follow-up visit, with health or social care services were reported as means (SD), with differences between the two groups assessed using a Student's *t*-test. Six-month resource-use totals were evaluated using an available-case analysis (i.e. for each treatment group, average resource use was summed over the three follow-up periods). Results are then presented as means together with 95% CIs, generated through 1000 bootstrap estimates. Mean differences were also estimated, as well as the 95% CI of the difference using bootstrapping.

Costs of providing the trial procedures

Time spent by participants in theatre was costed using Scottish information on theatre services,[45] excluding costs for medical, nursing and other staff, drugs and other supplies (as this information was collected directly by the trial). For participants undergoing standard chest tube talc slurry pleurodesis, we also excluded central sterile supply department costs, as all equipment used was disposable. Capital equipment (including video stack, thoracoscopes, light cable, pre-heater and tube inserts) costs used to perform the thoracoscopy-delivered talc poudrage were obtained directly from the manufacturer. To obtain an equivalent annual cost for all capital equipment, we depreciated the acquisition costs over their assumed 5-year lifetime, using an annual rate of 3.5%. To obtain per-minute costs, we assumed that this equipment would be used for 4 hours per week over 50 weeks per year.

Costs of staff time

This included the consultant physician, specialist registrar, nurse and health-care assistant and was valued using average salaries for that position.[40] Unit costs of disposables was valued using prices obtained from the *NHS Supply Chain*.[46] Costs of medications and sedation drugs were obtained from the *British National*

Formulary.[47] Finally, costs of investigations undertaken as part of the intervention, including CXRs and thoracic ultrasonography, were obtained from NHS reference costs.[41]

Total costs

Costs of the initial hospitalisation, and costs incurred between each follow-up visits, are presented as means (SD), with differences between the two patient groups assessed using a Student's *t*-test. Six-month total costs were evaluated using an available-case analysis (i.e. for each treatment group, average total costs were summed over the three follow-up periods), as well as initial hospitalisation and intervention costs. Results are then presented as means with 95% CIs, generated through 1000 bootstrap estimates. Mean differences were also estimated, as well as the 95% CI of the difference, using bootstrapping.

Cost-effectiveness

In order to evaluate if thoracoscopy-delivered talc poudrage was cost-effective when compared with standard chest tube talc slurry pleurodesis, we carried out an incremental analysis, with the mean cost difference between thoracoscopy-delivered talc poudrage and standard chest tube talc slurry pleurodesis divided by the mean QALY difference to give the ICER. As per NICE recommendations,[48] we judged an intervention to be cost-effective if the ICER was $\leq$ £20,000 per QALY gained.

However, given that average life expectancy in patients enrolled in the TAPPS trial was < 1 year, it could be argued that NICE's end-of-life criteria for assessing cost-effectiveness might apply.[49] As a result, in sensitivity analyses, we evaluated the impact of increasing the cost-effectiveness threshold to £50,000 per QALY gained.[50]

We used the non-parametric percentile method for calculating the CI around the ICER, using 1000 bootstrap estimates of the mean cost and QALY differences.[51] Results of the 1000 bootstrap estimates are also presented in the cost-effectiveness plane. We used the cost-effectiveness acceptability curve to show the probability that thoracoscopy-delivered talc poudrage is cost-effective at 6 months for the £20,000 and £50,000 per QALY NICE thresholds, and also for different values of the NHS's willingness to pay for an additional QALY.[52]

To account for the possibility that LATs performed during the trial were of a longer duration than those LATs that might be performed in clinical practice, we undertook a one-way sensitivity analysis to examine the impact on the results of shortening the duration of thoracoscopy-delivered talc poudrage by 10 minutes.

Multiple imputation

As the analysis of the TAPPS trial data were undertaken on an intention-to-treat basis, multiple imputation was used to impute missing cost and utility values.[53–55] As per recommended best practice, imputation was implemented separately by randomised treatment allocation.[56] Costs were imputed at the most disaggregated level at which the model would converge. As a result, we imputed values for general practice consultation costs (at practice, home and telephone); hospitalisation costs (outpatient visits, A&E and ambulance, inpatient stays and day cases); hospice and nursing costs (hospice stays, and hospice and other nurse visits); and other health-care costs (physiotherapy, occupational therapy, counselling and psychologist visits).

Rather than imputing missing responses for each of the five domains in the EQ-5D-5L, we imputed the overall EQ-5D-5L utility.[57] The imputation of costs and utility was conducted using predictive mean matching (i.e. imputes data from similar patients with complete data) to account for the skewed nature

of both cost and utility data. Imputation was conducted using age, sex, baseline utility levels and the trial minimisation criteria (i.e. type of underlying malignant disease and WHO/ECOG performance status). We generated 60 replacement values for each missing case, generating 60 imputed data sets.

Using the Stata 'mi estimate command', we obtained mean estimates of cost and utility and SD. Differences across patients groups were obtained using ordinary least squares regression using the 'mi estimate: reg' command.

Chapter 4 Main trial results

Recruitment

Recruitment took place between August 2012 and October 2017, with 17 centres contributing participants.

Table 4 shows the distribution of recruitment by site.

Flow of participants in the trial

The target of 330 participants was achieved, with 164 participants allocated to the control (slurry) arm and 166 participants to the intervention (poudrage) arm. A total of 159 (97.0%) and 161 (97%) participants, respectively, were included in the primary outcome analysis. Fourteen (8.5%) and 15 (9.0%) participants, respectively, withdrew during the 6-month follow-up period.

A comprehensive overview of participant flow, including screening activity, is given in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram in *Figure 4*.

TABLE 4 Recruitment by site

Site	Approval date	Final recruitment total
Taunton	2 November 2012	54
South Manchester	15 March 2013	38
Oxford	9 November 2012	30
Nottingham	22 October 2012	27
Bristol	26 September 2012	26
Glasgow	5 September 2014	26
King's Mill	23 October 2012	24
Cambridge	3 April 2013	22
Glan Clwyd	24 February 2015	19
Preston	9 January 2013	13
Doncaster	19 March 2014	13
St Thomas' (London)	18 December 2013	10
North Tees	26 June 2014	9
Medway	30 October 2012	7
Milton Keynes	24 October 2014	7
Aintree	2 September 2014	4
Birmingham	20 October 2014	1
Total	–	330

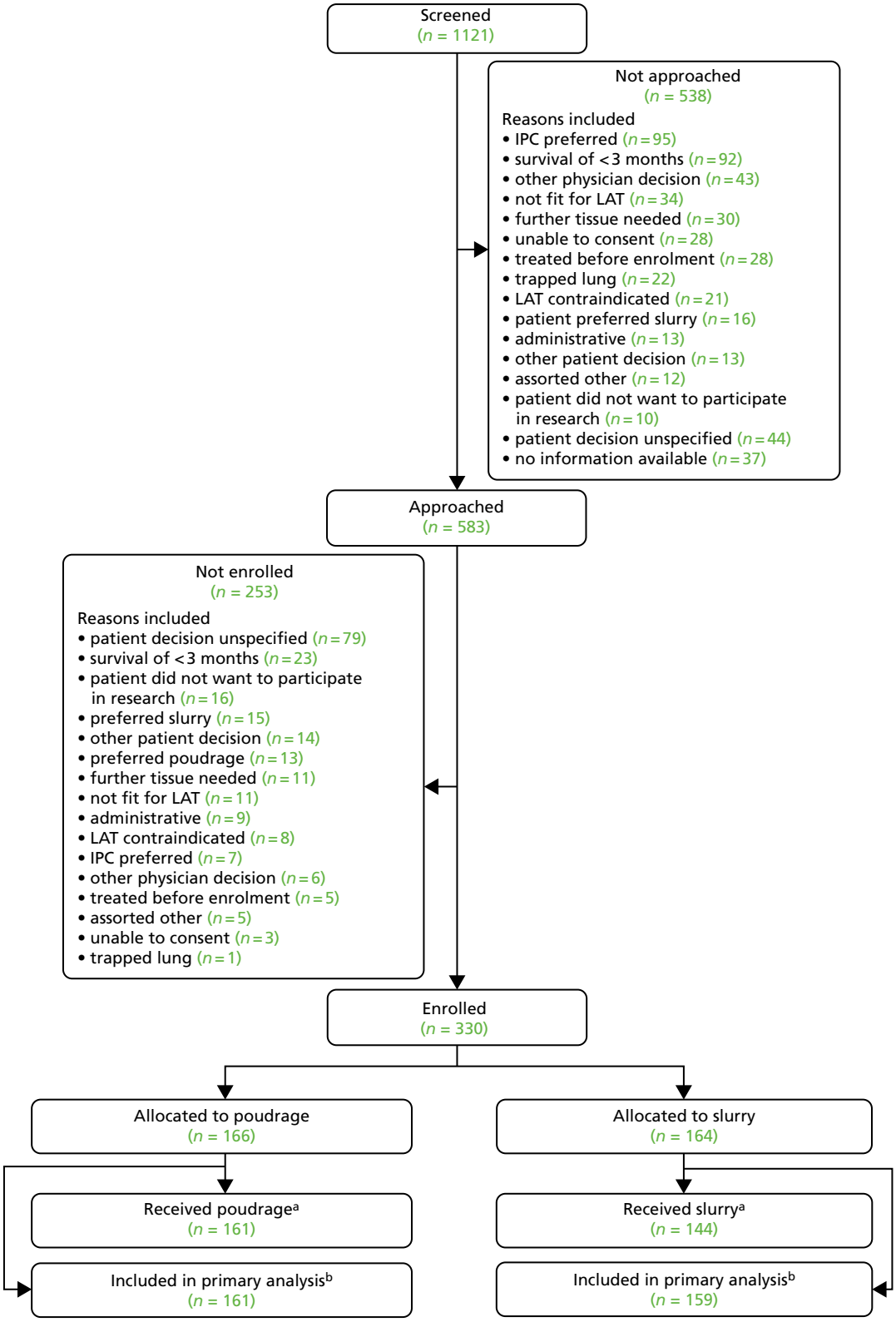

FIGURE 4 The trial CONSORT flow diagram. a, Reasons for not receiving allocated treatment: poudrage arm – thoracoscopy not attempted ($n = 2$), procedure abandoned before talc ($n = 2$), talc not given because of rapid lung expansion on coughing ($n = 1$); slurry arm – chest drain not attempted ($n = 2$), talc not given ($n = 18$) because of lung expansion ($n = 6$), lung entrapment ($n = 5$), excessive fluid production ($n = 1$), drain dislodgement ($n = 1$), early drain removal ($n = 1$), loculated pleural space ($n = 1$), missing data ($n = 3$); and b, patients were not included in the primary outcome analysis if there were no data available regarding pleurodesis failure at 90 days post randomisation.

Baseline characteristics

In general, both treatment groups were well matched at baseline. A higher proportion of participants in the control group (33/164, 20%) were noted to be receiving chemotherapy at enrolment than in the intervention group (15/166, 9%). The mean age at enrolment was 68 years in both groups. The majority of participants (79% control, 78% intervention) were of ECOG performance status 1 or 2. The commonest underlying cancer types were lung and breast cancer.

Table 5 describes the full set of baseline characteristics.

TABLE 5 Baseline characteristics

Characteristic	Treatment arm, summary measure		Treatment arm, number with missing data	
	Thoracoscopy and poudrage	Chest drain and slurry	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
Age (years), mean (SD)	68 (11)	68 (12)	0 (0)	0 (0)
Chest pain (VAS), mean (SD)	17 (23)	18 (25)	1 (1)	1 (1)
Breathlessness (VAS), mean (SD)	53 (29)	53 (33)	1 (1)	1 (1)
Percentage radiographic (CXR) pleural opacification, mean (SD)	54 (20)	47 (20)	129 (78)	127 (77)
Blood measurements				
Hb, mean (SD)	131 (20)	129 (19)	3 (2)	3 (2)
Sodium, mean (SD)	136 (10)	137 (4.0)	3 (2)	2 (1)
INR, median (IQR)	1.0 (1.0–1.1)	1.0 (1.0–1.1)	38 (23)	38 (23)
WCC, mean (SD)	9.8 (14)	9.5 (9.4)	2 (1)	3 (2)
Potassium, mean (SD)	5.0 (5.1)	4.5 (2.2)	6 (4)	7 (4)
APTT, mean (SD)	27 (14)	28 (12)	30 (18)	22 (13)
Platelets, mean (SD)	342 (119)	334 (124)	3 (2)	3 (2)
Urea, mean (SD)	5.8 (3.0)	6.6 (7.6)	5 (3)	9 (5)
CRP, mean (SD)	46 (60)	46 (53)	35 (21)	26 (16)
Creatinine, mean (SD)	74 (29)	75 (28)	4 (2)	2 (1)
General categorical variables,* n *(%)				
Female	96 (58)	85 (52)	0 (0)	0 (0)
Smoking status			1 (1)	0 (0)
Current smoker	13 (8)	12 (7)		
Ex-smoker	104 (63)	98 (60)		
Never smoker	48 (29)	54 (33)		
WHO score			1 (1)	0 (0)
0	17 (10)	18 (11)		
1	82 (50)	81 (49)		
2	46 (28)	49 (30)		
3	20 (12)	16 (10)		
Effusion on right-hand side	91 (55)	91 (55)	0 (0)	0 (0)

continued

TABLE 5 Baseline characteristics (*continued*)

Characteristic	Treatment arm, summary measure		Treatment arm, number with missing data	
	Thoracoscopy and poudrage	Chest drain and slurry	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
Pleural intervention in previous 3 months	117 (70)	121 (74)	0 (0)	0 (0)
Pleurodesis attempt in previous month	2 (1)	3 (2)	0 (0)	0 (0)
Length of symptoms (weeks)			0 (0)	0 (0)
< 1	5 (3)	6 (4)		
1–3	40 (24)	35 (21)		
> 3	121 (73)	123 (75)		
Percentage radiographic (CXR) pleural opacification			129 (78)	127 (77)
1–24	3 (8)	4 (11)		
25–49	15 (41)	18 (49)		
≥ 50	19 (51)	15 (41)		
Underlying cancer type			0 (0)	0 (0)
Lung	59 (36)	54 (33)		
Mesothelioma	15 (9)	19 (12)		
Breast	50 (30)	49 (30)		
Ovarian	6 (4)	7 (4)		
Lymphoma	3 (2)	2 (1)		
Upper GI	4 (2)	4 (2)		
Lower GI	6 (4)	9 (5)		
Renal	5 (3)	11 (7)		
Other	15 (9)	5 (3)		
Unknown	3 (2)	4 (2)		
Analgesia				
Oral steroids	22 (13)	24 (15)	0 (0)	1 (1)
NSAIDs	21 (13)	29 (18)	0 (0)	1 (1)
Analgesic	118 (71)	107 (66)	0 (0)	1 (1)
Cancer treatment				
One or more anticancer treatment	44 (27)	55 (34)	0 (0)	1 (1)
Radiotherapy	48 (29)	40 (25)	0 (0)	1 (1)
Cancer-modulating hormone therapy	27 (16)	17 (10)	0 (0)	1 (1)
Anticancer monoclonal antibodies	5 (3)	6 (4)	0 (0)	1 (1)
Chemotherapy	15 (9)	33 (20)	0 (0)	2 (1)
Other anticancer therapy	2 (1)	6 (4)	0 (0)	1 (1)
Anticoagulant therapy	29 (17)	35 (21)	0 (0)	1 (1)

TABLE 5 Baseline characteristics (*continued*)

Characteristic	Treatment arm, summary measure		Treatment arm, number with missing data	
	Thoracoscopy and poudrage	Chest drain and slurry	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
Comorbidities				
COPD/asthma	20 (12)	18 (11)	0 (0)	0 (0)
Interstitial lung disease	1 (1)	1 (1)	0 (0)	1 (1)
Bronchiectasis	1 (1)	2 (1)	0 (0)	0 (0)
Pulmonary hypertension	0 (0)	0 (0)	0 (0)	0 (0)
Other respiratory disease	4 (2)	5 (3)	0 (0)	0 (0)
Ischaemic heart disease	11 (7)	13 (8)	1 (1)	0 (0)
Atrial fibrillation	14 (8)	10 (6)	0 (0)	0 (0)
Heart failure	1 (1)	2 (1)	0 (0)	0 (0)
Other cardiac disease	27 (16)	19 (12)	0 (0)	0 (0)
Minimisation factors*, n *(%)				
Underlying malignancy			0 (0)	0 (0)
Lung	57 (34)	57 (35)		
Breast	50 (30)	48 (29)		
Mesothelioma	16 (10)	17 (10)		
Other	43 (26)	42 (26)		
Grouped WHO score			0 (0)	0 (0)
0–1	99 (60)	99 (60)		
2–3	67 (40)	65 (40)		

APTT, activated partial thromboplastin time; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GI, gastrointestinal; Hb, haemoglobin; INR, international normalised ratio; IQR, interquartile range; NSAID, non-steroidal anti-inflammatory drug; WCC, white cell count.

Adherence to interventions

A total of 144 out of 164 (88%) of participants received their treatment as intended in the control arm, compared with 161 out of 166 (97%) of participants in the intervention arm. Of those patients in the control arm, 18 out of 20 participants did not receive talc after chest drain insertion.

A summary of treatment adherence (and the reasons for non-adherence) can be found in *Tables 6* and *7*.

TABLE 6 Summary of treatment adherence

Treatment adherence	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
Treatment given as intended		
No	5 (3)	20 (12)
Yes	161 (97)	144 (88)
Reason treatment not given as intended		
Procedure not attempted	2 (1)	2 (1)
Procedure abandoned	2 (1)	0 (0)
Talc not given	1 (1)	18 (11)

TABLE 7 Reasons (and numbers of) patients not given talc

Reason	Treatment arm (*n*)	
	Thoracoscopy and poudrage (*N* = 1)	Chest drain and slurry (*N* = 18)
Poor lung expansion/trapped lung	0	9
Excessive pleural production	0	1
Other[a]	1	5
Missing	0	3

a Intervention arm: rapid lung reinflation on coughing (*n* = 1). Control arm: drain fell out (*n* = 1), clinical decision (*n* = 1), patient deterioration (*n* = 1), drain removed (*n* = 1), pleural space complex/septated (*n* = 1).

Details of interventions

The median [interquartile range (IQR)] duration of the control procedure was 30 (IQR 20–40) minutes. The median duration of the intervention procedure was 49 (IQR 40–60) minutes. A total of 110 of 164 (67%) of LAT procedures, compared with 62 of 163 (38%) control procedures, were performed by consultant-grade doctors. A total of 111 of 153 (73%) and 120 of 161 (75%) of participants in the control and intervention groups, respectively, had thoracic suction applied during their post-procedure period. A comprehensive summary of intervention details can be found in *Table 8*.

The frequency of complications during both trial procedures was low. Of note, 12 out of 161 (7%) and 8 out of 161 (5%) participants in the intervention arm were documented as experiencing new hypotension and a drop in transcutaneous oxygen saturations, respectively, after talc was given. No participants in the control arm experienced either of these events either before or after talc was given. A comprehensive summary of recorded procedural complications can be found in *Table 9*.

TABLE 8 Details of allocated treatments

Characteristic	Treatment arm, summary measure		Treatment arm, number of participants without data	
	Thoracoscopy and poudrage	Chest drain and slurry	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
Duration of procedure (minutes), mean (SD)	51 (22)	32 (13)	15 (9)	26 (16)
Grade of operator, *n* (%)			2 (1)	1 (1)
CT1/CT2	0 (0)	10 (6)		
Consultant	110 (67)	62 (38)		
F1/F2	0 (0)	4 (2)		
Other	0 (0)	9 (6)		
Registrar	54 (33)	78 (48)		
Total fluid (ml) drained as an inpatient, mean (SD)	3442 (1831)	2890 (2094)	11 (7)	10 (6)
Evidence of lung entrapment: 18–24 hours, *n* (%)			60 (36)	55 (34)
None	85 (80)	90 (83)		
Mild	8 (8)	8 (7)		
Moderate	8 (8)	7 (6)		
Severe	5 (5)	4 (4)		

TABLE 8 Details of allocated treatments (*continued*)

Characteristic	Treatment arm, summary measure		Treatment arm, number of participants without data	
	Thoracoscopy and poudrage	Chest drain and slurry	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
Evidence of lung entrapment: discharge, *n* (%)			61 (37)	66 (40)
None	92 (88)	90 (92)		
Mild	1 (1)	4 (4)		
Moderate	4 (4)	1 (1)		
Severe	8 (8)	3 (3)		
Thoracic suction used, *n* (%)	120 (75)	111 (73)	5 (3)	11 (7)
Time drain removed, *n* (%)			13 (8)	7 (4)
On time	113 (74)	126 (80)		
Early	12 (8)	11 (7)		
Late	28 (18)	20 (13)		

CT1, core medical trainee 1; CT2, core medical trainee 2; F1, Foundation year 1 doctor; F2, Foundation year 2 doctor.

TABLE 9 Summary of treatment complications

Complication	Treatment summary measure, *n* (%)	
	Thoracoscopy and poudrage ($N = 166$)	Chest drain and slurry ($N = 164$)
During procedure	164 with data available	162 with data available
Bleeding	1 (1)	0 (0)
Significant cough	4 (2)	2 (1)
Syncope	2 (1)	1 (1)
Significant pain	0 (0)	3 (2)
Pleural space not entered	1 (1)	0 (0)
New hypoxia	2 (1)	0 (0)
Dysrhythmia	0 (0)	0 (0)
New hypotension	4 (2)	0 (0)
Other	3 (2)	1 (1)
After talc	161 with data available	144 with data available
Nausea	3 (2)	2 (1)
Respiratory distress	0 (0)	0 (0)
GCS score drop of > 2 points	0 (0)	0 (0)
Uncontrolled pain	7 (4)	1 (1)
New hypotension	12 (7)	0 (0)
Saturation drop	8 (5)	0 (0)
Allergic reaction	0 (0)	0 (0)
New confusion	0 (0)	0 (0)
Bleeding	0 (0)	0 (0)
Other	6 (4)	5 (3)

GCS, Glasgow Coma Scale.

Primary outcome

Treatment efficacy at 90 days

A total of 97% of participants in both arms (159/164 control, 161/166 intervention) were included in the primary outcome analysis. No significant difference in pleurodesis failure was observed between the treatment groups at 90 days, with failure rates of 22% (36/161) and 24% (38/159) noted in the poudrage and slurry groups, respectively [adjusted odds ratio (OR) 0.91, 95% CI 0.54 to 1.55; $p = 0.74$].

Sensitivity analysis

Sensitivity analyses for the primary outcome evaluated how sensitive results were to departures from the missing-at-random assumption described above by conducting various missing-not-at-random analyses; these analyses made different assumptions about the event rates for participants with missing data in the control and intervention arms. Results are shown in *Figure 5*, which shows the treatment effect as a difference in proportions. Results were very robust to alternative assumptions regarding the missing data.

Subgroup analyses

We found moderate evidence of a subgroup effect between participants taking oral steroids at baseline and those participants not taking oral steroids (*p*-value for interaction 0.04). In the subgroup on oral steroids, there was a lower rate of pleurodesis failure (6/24, 25%) in the control group than in the intervention group (10/20, 50%) (adjusted OR 3.13, 95% CI 0.84 to 11.61). Conversely, in the subgroup not on oral steroids, there was a slightly higher rate of pleurodesis failure in the control arm (32/134, 24%) than in the intervention arm (26/141, 19%) (adjusted OR 0.71, 95% CI 0.39 to 1.29).

No significant interaction effects were found in the use of anticancer therapy at baseline, previous attempts at pleurodesis, baseline performance score or type of underlying malignancy. All prespecified subgroup analysis results can be found in *Table 10*.

All treatment effects are adjusted for the minimisation factors.

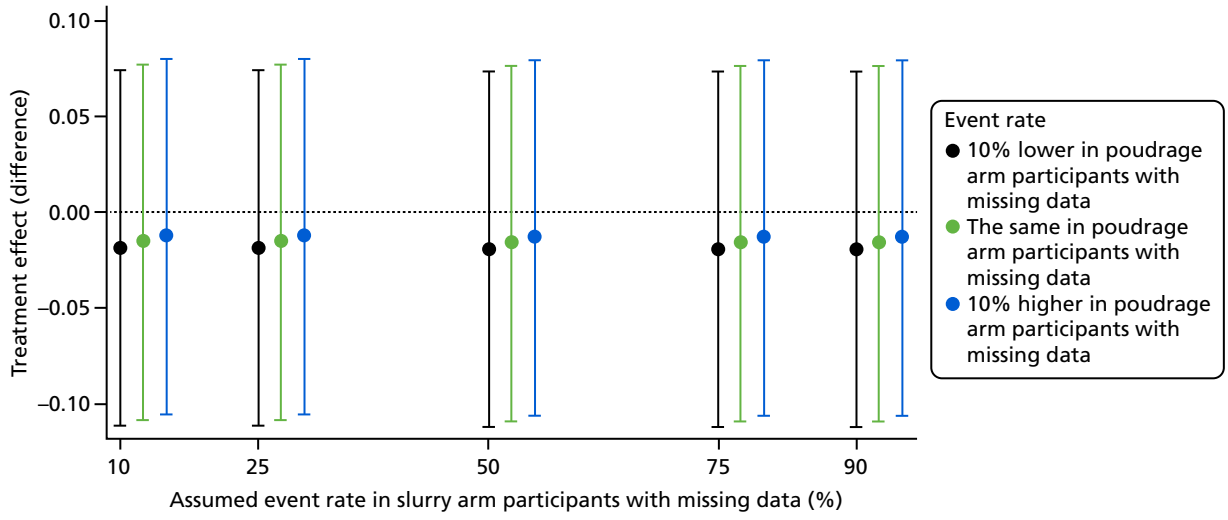

FIGURE 5 Sensitivity analysis for the primary outcome.

TABLE 10 Prespecified subgroup analyses for the primary outcome

Subgroup	Treatment arm, summary measure, *n/N* (%)		Adjusted OR (95% CI)	*p*-value for interaction with treatment
	Thoracoscopy and poudrage	Chest drain and slurry		
Anticancer therapy at baseline				
No	25/118 (21)	29/105 (28)	0.65 (0.35 to 1.23)	
Yes	11/43 (26)	9/53 (17)	1.96 (0.71 to 5.45)	0.08
Attempt at pleurodesis in previous month				
No	34/159 (21)	38/156 (24)	0.85 (0.50 to 1.45)	
Yes	0/2 (0)	0/3 (0)	Not estimated	Not estimated
On steroids at baseline				
No	26/141 (18)	32/134 (24)	0.71 (0.39 to 1.29)	
Yes	10/20 (50)	6/24 (25)	3.13 (0.84 to 11.61)	0.04
WHO score				
0	4/15 (27)	0/16 (0)	Not estimated	
1	18/82 (22)	23/80 (29)	0.68 (0.33 to 1.42)	
2	12/44 (27)	11/48 (23)	1.37 (0.52 to 3.58)	
3	2/20 (10)	4/15 (27)	0.29 (0.04 to 1.91)	0.29
Primary malignancy				
Lung	10/55 (18)	16/56 (29)	0.55 (0.23 to 1.36)	
Breast	13/49 (27)	11/46 (24)	1.15 (0.46 to 2.92)	
Mesothelioma	7/16 (44)	6/16 (38)	1.31 (0.32 to 5.38)	
Other	6/41 (15)	5/41 (12)	1.23 (0.34 to 4.39)	0.60

Secondary outcomes

Secondary outcome results are summarised in *Table 11*. No statistically significant differences were seen in any outcome at any time point. *Figure 6* demonstrates the Kaplan–Meier plot for pleurodesis across all time points, with the reasons for pleurodesis failure given in *Table 12*. Results relating to quality-of-life secondary outcomes can be found in *Chapter 5*.

TABLE 11 Summary of secondary outcomes

Outcome	Treatment arm, summary measure (%)		Adjusted treatment effect estimate (95% CI)	*p*-value	Treatment arm, number of patients with data available (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)			Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
Pleurodesis failure (30 days), *n* (%)	16 (10)	22 (14)	0.69 (0.34 to 1.37)	0.29	161 (97)	159 (97)
Pleurodesis failure (180 days), *n* (%)	46 (29)	44 (28)	1.05 (0.63 to 1.73)	0.86	161 (97)	159 (97)
Time to pleurodesis failure,[a] median (IQR)	NR (91–NR)	NR (80–NR)	1.01 (0.67 to 1.52)	0.98	161 (97)	159 (97)
All-cause mortality (180 days), *n* (%)	66 (40)	68 (42)	0.91 (0.58 to 1.44)	0.70	165 (99)	163 (99)
Nights as hospital inpatient within 90 days, mean (SD)	12 (13)	11 (10)	1.11 (0.89 to 1.37)	0.35	165 (99)	162 (99)
Thoracic pain (VAS),[b] mean (SD) change from baseline					142 (86)	146 (89)
7 days	1.0 (25)	2.3 (28)	–1.2 (–6.9 to 4.6)	0.69		
30 days	–1.5 (25)	–5.6 (26)	1.2 (–3.5 to 6.0)	0.61		
90 days	–2.5 (23)	–6.9 (24)	0.5 (–4.8 to 5.8)	0.85		
180 days	–2.0 (23)	–6.2 (23)	0.8 (–4.6 to 6.2)	0.78		
Breathlessness (VAS),[b] mean (SD) change from baseline					142 (86)	146 (89)
7 days	–31 (32)	–29 (35)	–2.0 (–8.0 to 4.0)	0.51		
30 days	–28 (32)	–23 (39)	–4.4 (–11.1 to 2.3)	0.20		
90 days	–25 (35)	–29 (36)	2.1 (–5.4 to 9.6)	0.58		
180 days	–30 (33)	–29 (43)	–3.8 (–12.7 to 5.2)	0.41		
Percentage radiographic pleural opacification, mean (SD)					125 (75)	115 (70)
Drain removal	16 (12)	17 (15)	–0.8 (–4.5 to 2.9)	0.66		
1 month	25 (19)	26 (18)	–1.5 (–6.7 to 3.7)	0.58		
3 months	20 (19)	21 (19)	–2.5 (–8.9 to 3.9)	0.45		
6 months	17 (14)	16 (13)	–0.8 (–6.7 to 5.1)	0.79		

NR, not reached.

a 49/159 (31%) of participants in the control group and 42/161 (26%) participants in the intervention group died before experiencing pleurodesis failure, and 44 (28%) and 46 (29%) participants in the control and intervention groups, respectively, experienced pleurodesis failure within 180 days of randomisation. The adjusted hazard ratio from a post hoc Cox model that does not incorporate mortality as a competed risk was 1.01 (0.67 to 1.52).

b Analysis is of outcome adjusted for baseline measure.

Notes

All treatment effects are difference in means, except for pleurodesis failure and all-cause mortality (ORs); time to pleurodesis (hazard ratio) and nights in hospital (rate ratio). All treatment effects are adjusted for the minimisation factors.

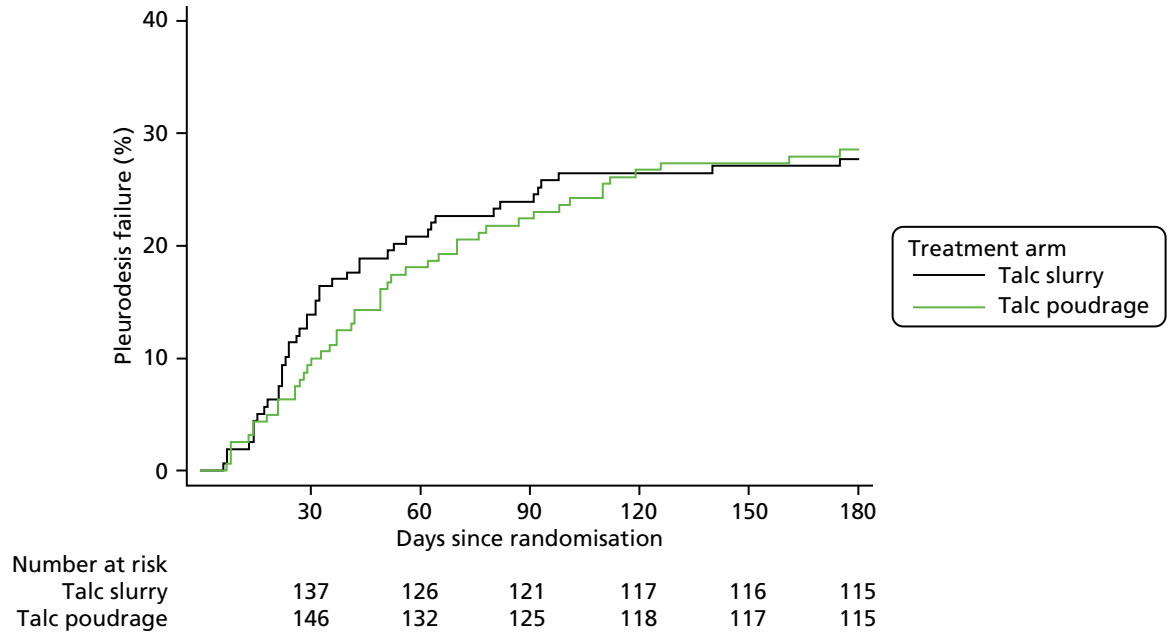

FIGURE 6 Kaplan–Meier plot for pleurodesis failure.

TABLE 12 Reasons for pleurodesis failure (all time points)

Mode of pleurodesis failure	Treatment arm (*n*)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
Pleurodesis failure (90 days) (primary outcome)		
Therapeutic aspiration of ≥ 100 ml	12	9
Insertion of intercostal drain for fluid drainage	7	7
Insertion of IPC	14	17
Medical/surgical thoracoscopy	1	0
Procedure required, but not done	2	5
Pleurodesis failure (30 days)		
Therapeutic aspiration of ≥ 100 ml	6	7
Insertion of intercostal drain for fluid drainage	3	4
Insertion of IPC	6	7
Medical/surgical thoracoscopy	0	0
Procedure required, but not done	1	4
Pleurodesis failure (180 days)		
Therapeutic aspiration of ≥ 100 ml	16	12
Insertion of intercostal drain for fluid drainage	8	8
Insertion of IPC	17	19
Medical/surgical thoracoscopy	2	0
Procedure required, but not done	3	5

Missing data summaries for relevant secondary outcomes can be found in *Tables 13–15*.

Figure 7 demonstrates the recorded time to mortality in both groups and *Table 10* shows the reasons for pleurodesis failure at both 30 and 90 days.

TABLE 13 Summary of missing data for thoracic pain VAS

Time point	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
7 days	58 (35)	66 (40)
30 days	43 (26)	40 (24)
90 days	75 (45)	71 (43)
180 days	98 (59)	95 (58)
At least one measurement available	142 (86)	146 (89)

TABLE 14 Summary of missing data for dyspnoea VAS

Time point	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
7 days	60 (36)	65 (40)
30 days	43 (26)	40 (24)
90 days	75 (45)	71 (43)
180 days	98 (59)	96 (59)
At least one measurement available	142 (86)	146 (89)

TABLE 15 Summary of missing data for percentage radiographic pleural opacification[a]

Time point	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
Drain removal	61 (37)	66 (40)
1 month	77 (46)	88 (54)
3 months	101 (61)	117 (71)
6 months	131 (79)	127 (77)
At least one measurement available	125 (75)	115 (70)

a These summaries also represent the number of missing data for the exploratory outcome of categorical version of percentage radiographic pleural opacification.

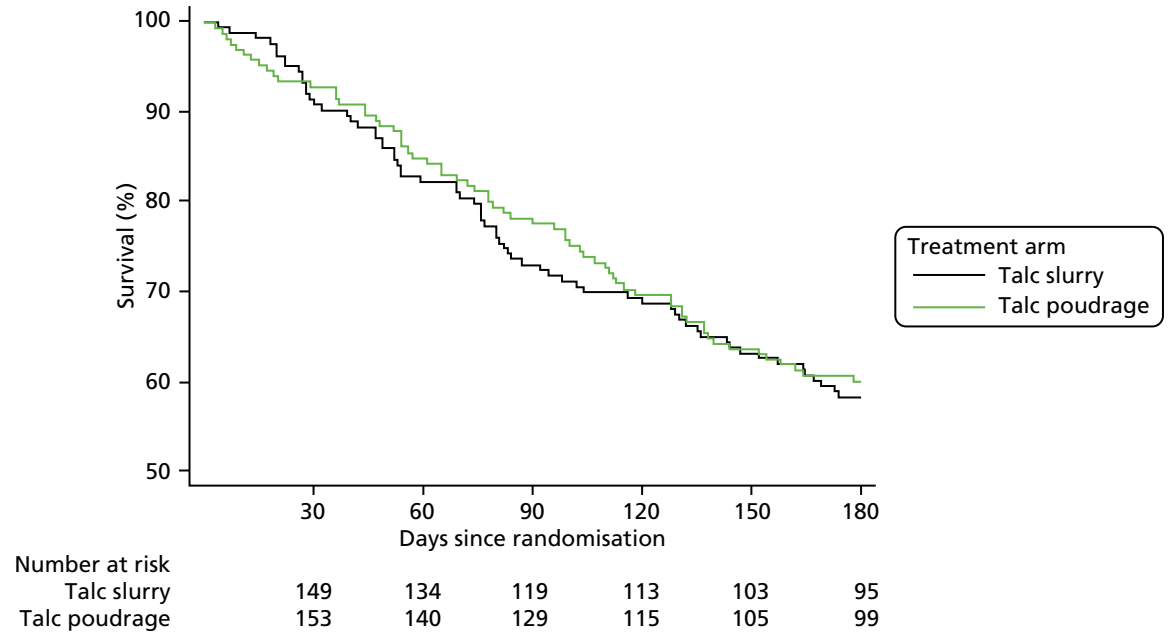

FIGURE 7 Time to mortality. Reproduced with permission from *JAMA*. 2020. 323:60–69. Copyright©2020 American Medical Association. All rights reserved.

Exploratory outcomes

The results for the exploratory outcomes can be found in *Tables 16–18*. Analysis of lung entrapment was not performed as the outcome was the same across all participants in both treatment arms.

Post hoc summaries and analyses

Treatment delay and initial inpatient stay

Delay from randomisation to allocated treatment is summarised in *Table 19*. A total of 18 out of 164 (11.0%) participants in the control arm waited for ≥ 1 day, whereas 38 out of 164 (23.2%) participants in the intervention group waited for ≥ 1 day.

There was no difference between the groups in the mean length of initial hospital stay from randomisation to discharge [control 5.7 (SD 5.6) days vs. intervention 5.8 (SD 9.7) days, rate ratio 1.00, 95% CI 0.85 to 1.19; $p = 0.99$].

Talc administration

A total of 18 out of 164 (11.0%) participants in the control arm did not receive talc slurry following drain insertion. One out of 166 (0.6%) participants in the intervention arm did not receive talc despite undergoing LAT. The reasons for not receiving talc, as well as the clinical outcomes of these participants, are summarised in *Tables 7* and *20*.

Thoracic suction

Limited data were available regarding time spent on thoracic suction (control 84/164, 51.2% vs. intervention 90/166, 54.2%). Those participants in the control arm spent a median of 26.3 (IQR 21.0–46.7) hours on suction compared with a median of 45.7 (IQR 36.0–71.0) hours in the intervention group.

Early symptom scores

Figures 8 and *9* show the between-group differences in dyspnoea and chest pain over the first 7 days post randomisation.

TABLE 16 Categorical version of percentage radiographic (CXR) pleural opacification: summary measures

Time point and degree of specification	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
Drain removal/discharge	105 (63) included	98 (60) included
No fluid visible	18 (17)	12 (12)
1–24% opacification	66 (63)	58 (59)
25–49% opacification	20 (19)	23 (23)
≥ 50% opacification	1 (1)	5 (5)
1 month	89 (54) included	76 (46) included
No fluid visible	7 (8)	1 (1)
1–24% opacification	44 (49)	42 (55)
25–49% opacification	29 (33)	27 (36)
≥ 50% opacification	9 (10)	6 (8)
3 months	65 (39) included	47 (29) included
No fluid visible	8 (12)	6 (13)
1–24% opacification	36 (55)	25 (53)
25–49% opacification	14 (22)	14 (30)
≥ 50% opacification	7 (11)	2 (4)
6 months	35 (21) included	37 (23) included
No fluid visible	5 (14)	8 (22)
1–24% opacification	22 (63)	21 (57)
25–49% opacification	6 (17)	7 (19)
≥ 50% opacification	2 (6)	1 (3)

TABLE 17 Categorical version of percentage radiographic (CXR) pleural opacification: analysis results

	Common OR (95% CI)	*p*-value
Treatment effect across all time points[a]	0.77 (0.45 to 1.34)	0.36

a 115 (70) and 125 (75) participants in the control and intervention groups, respectively, included in analysis.

TABLE 18 Degree of visible lung entrapment on CXR at 6 months: summary measures

Time point and degree of entrapment	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
6 months	35 (21) included	37 (23) included
No lung entrapment	35 (100)	37 (100)
Minor lung entrapment (1–24% unexpanded lung)	0 (0)	0 (0)
Moderate lung entrapment (25–49% unexpanded lung)	0 (0)	0 (0)
Severe lung entrapment (≥ 50% unexpanded lung)	0 (0)	0 (0)

TABLE 19 Summary of delay from randomisation to allocated procedure

Number of days	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)[a]	Chest drain and slurry (*N* = 164)[b]
0	126 (77)	146 (89)
1	20 (12)	17 (10)
2	11 (7)	1 (1)
3	5 (3)	0 (0)
4	0 (0)	0 (0)
5	1 (1)	0 (0)
6	1 (1)	0 (0)

a 164 (99) included.
b 164 (100) included.

TABLE 20 Clinical outcomes in patients who did not receive talc

Outcome	Treatment arm, *n/N*	
	Thoracoscopy and poudrage (*N* = 1)	Chest drain and slurry (*N* = 18)
Pleurodesis failure 90 days (primary outcome)[a]	0/1	6/16
Mortality within 180 days	0/1	13/18

a Outcome missing for two patients in control arm.

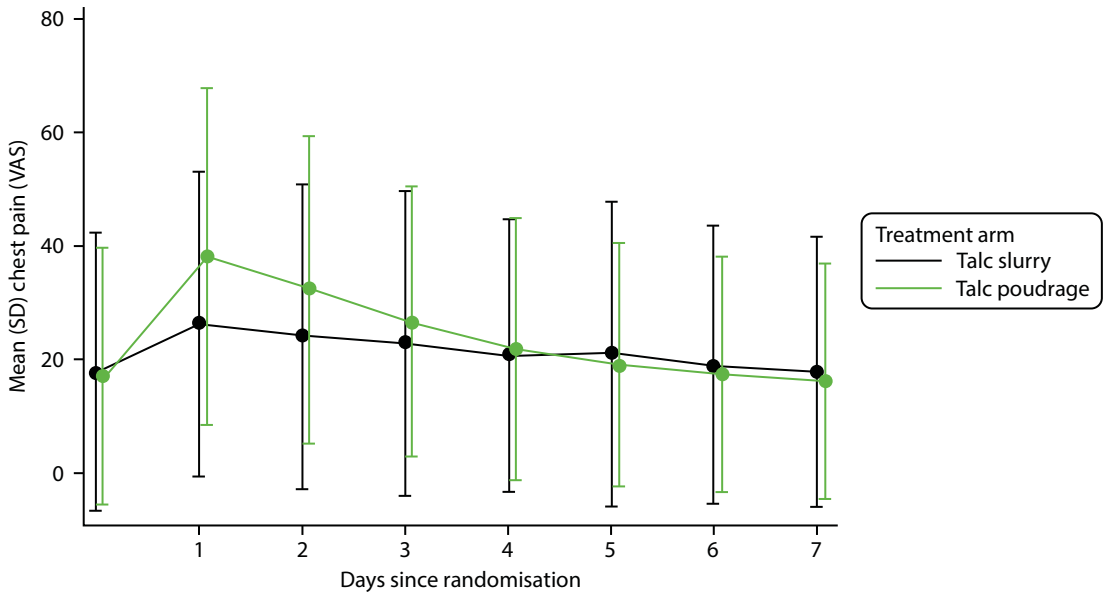

FIGURE 8 Thoracic pain VAS over the first 7 days post randomisation.

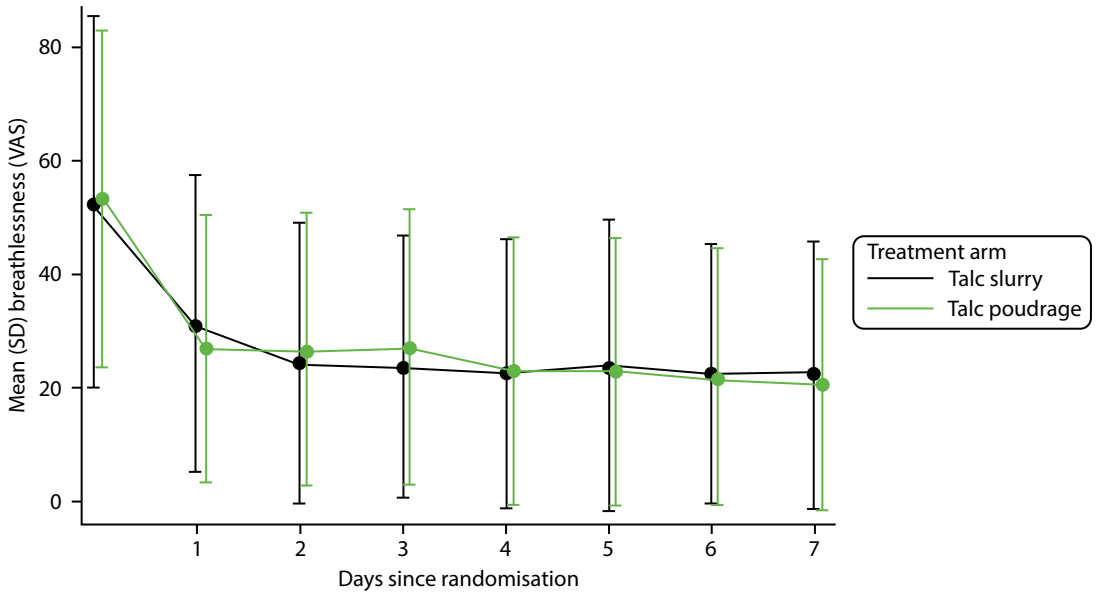

FIGURE 9 Dyspnoea VAS over the first 7 days post randomisation.

Adverse events and serious adverse events

Adverse events

A summary of all recorded AEs can be found in *Table 21*.

In the control arm, 80 out of 164 (49%) participants experienced at least one AE compared with 91 out of 166 (55%) participants in the intervention arm. A summary of the number of participants experiencing multiple events can be found in *Table 22*.

There was no significant difference between the groups in the number of AEs recorded at 7, 30 or 180 days (*Table 23*).

Serious adverse events

A summary of all recorded SAEs can be found in *Table 24*.

TABLE 21 Summary of AEs by type

AE	Treatment arm (*n*)	
	Thoracoscopy and poudrage (*N* = 179)	Chest drain and slurry (*N* = 152)
Accidental injury	3	2
Anaemia	10	4
Cardiac arrhythmia	2	2
Cerebrovascular event	0	2
Disease progression: death	7	5
Disease progression: dyspnoea due to fluid	23	20
Disease progression: dyspnoea not due to fluid	4	4
Disease progression: metastatic disease	7	5
Disease progression: nausea/vomiting	2	2
Disease progression: other	2	1

TABLE 21 Summary of AEs by type (*continued*)

AE	Treatment arm (*n*)	
	Thoracoscopy and poudrage (*N* = 179)	Chest drain and slurry (*N* = 152)
Disease progression: pain	0	3
Drain blockage (IPC)	1	1
Drain dislodgement/accidental removal	2	9
Lung entrapment	4	1
Medication/chemotherapy side effect	9	13
Non-chest infection	7	5
Other abnormal blood tests	1	0
Other AE/unspecified	1	0
Other pleural intervention related: pleural infection	0	2
Other pleural intervention related: pneumothorax/bronchopleural fistula	15	18
Other venous thromboembolic event	0	2
Pneumonia/chest infection	25	19
Pulmonary embolism	7	9
Trial intervention related: other/unspecified	10	7
Trial intervention related: bleeding	2	1
Trial intervention related: cough	1	0
Trial intervention related: hypoxia	4	0
Trial intervention related: pain	9	6
Trial intervention related: pleural infection	6	0
Trial intervention related: pneumothorax/bronchopleural fistula	3	4
Trial intervention related: subcutaneous infection	3	3
Trial intervention related: surgical emphysema	9	2

TABLE 22 Summary of AEs by frequency of occurrence

Summary measure	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
At least one AE	91 (55)	80 (49)
Number of AEs per patient		
0	75 (45)	84 (51)
1	43 (26)	39 (24)
2	27 (16)	24 (15)
3	7 (4)	7 (4)
4	11 (7)	7 (4)
5	2 (1)	2 (1)
6	0 (0)	1 (1)
7	1 (1)	0 (0)

TABLE 23 Analysis of AEs by trial time point

AE by time point	Treatment arm, summary measure, *n* (%)		OR (95% CI)	*p*-value
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)		
AE within 7 days	50 (30)	43 (26)	1.21 (0.74 to 1.97)	0.45
AE within 30 days	61 (37)	60 (37)	1.00 (0.63 to 1.57)	0.99
AE within 180 days	89 (54)	77 (47)	1.31 (0.84 to 2.03)	0.23

TABLE 24 Summary of SAEs by type

SAE	Treatment arm (*n*)	
	Thoracoscopy and poudrage (*N* = 64)	Chest drain and slurry (*N* = 54)
Accidental injury	0	1
Anaemia	1	1
Cerebrovascular event	0	2
Disease progression: death	11	12
Disease progression: dyspnoea due to fluid	6	8
Disease progression: dyspnoea not due to fluid	4	1
Disease progression: metastatic disease	6	1
Disease progression: nausea/vomiting	2	0
Drain blockage (non-IPC)	1	1
Drain dislodgement/accidental removal	0	1
Lung entrapment	1	0
Medication/chemotherapy side effect	1	2
Non-chest infection	2	0
Other abnormal blood tests	1	2
Other AE/unspecified	3	1
Other venous thromboembolic event	0	1
Pneumonia/chest infection	10	7
Pulmonary embolism	2	3
Trial intervention related: other/unspecified	2	1
Trial intervention related: bleeding	1	2
Trial intervention related: hypoxia	4	0
Trial intervention related: pain	0	1
Trial intervention related: pleural infection	5	2
Trial intervention related: pneumothorax/ bronchopleural fistula	0	3
Trial intervention related: subcutaneous infection	1	1

In the control arm, 44 out of 164 (27%) participants experienced at least one SAE compared with 46 out of 166 (28%) participants in the intervention arm. A summary of the number of participants experiencing multiple events can be found in *Table 25*.

There was no significant difference between the groups in the number of SAEs recorded at 7, 30 or 180 days (*Table 26*).

TABLE 25 Summary of SAEs by frequency of occurrence

SAE	Treatment arm, *n* (%)	
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)
At least one SAE	46 (28)	44 (27)
Number of SAEs per patient		
0	120 (72)	120 (73)
1	30 (18)	35 (21)
2	14 (8)	8 (5)
3	2 (1)	1 (1)

TABLE 26 Analysis of SAEs by trial time point

SAE by time point	Treatment arm, summary measure, *n* (%)		OR (95% CI)	*p*-value
	Thoracoscopy and poudrage (*N* = 166)	Chest drain and slurry (*N* = 164)		
SAE within 7 days	17 (10)	15 (9)	1.13 (0.54 to 2.35)	0.75
SAE within 30 days	26 (16)	26 (16)	0.98 (0.54 to 1.78)	0.94
SAE within 180 days	46 (28)	44 (27)	1.04 (0.64 to 1.70)	0.88

Chapter 5 Health economic evaluation results

Quality of life

Responses to the EQ-5D-5L are reported in *Appendix 2* (see *Table 34*). These responses were then converted into utilities (*Table 27*). There were no statistically significant differences in utilities or VAS scores at any of the three follow-up time points.

Summary scores for each of the eight domains of the SF-36 are presented in *Appendix 2* (see *Table 35*). There were no statistically significant differences in scores between the two groups at any of the three follow-up time points. In addition, there were no differences in the two summary scores (physical component score and mental health component score). As with the EQ-5D-5L, there were no differences in SF-6D utilities between the two patient groups in any of the follow-up time points (see *Table 27*).

Survival data were combined with EQ-5D-5L utilities to estimate QALYs at 6 months after randomisation. Patients randomised to thoracoscopy-delivered talc poudrage gained, over 6 months, an average of 0.246 (95% CI 0.227 to 0.263) QALYs compared with 0.239 (95% CI 0.217 to 0.258) in those patients randomised to standard chest tube talc slurry pleurodesis. This resulted in a non-significant increase of 0.007 (95% CI difference –0.019 to 0.034) QALYs in patients randomised to thoracoscopy-delivered talc poudrage.

TABLE 27 The EQ-5D-5L, VAS and SF-6D utilities

Quality-of-life measure	Treatment arm, mean (SD), *n*		$p > \|z\|$	Mean difference (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry		
EQ-5D-5L utility				
Randomisation	0.57 (0.26), 163	0.55 (0.26), 164	0.571	0.02 (–0.04 to 0.07)
1 month	0.60 (0.26), 132	0.60 (0.27), 132	0.892	0.00 (–0.06 to 0.07)
3 months	0.60 (0.29), 95	0.65 (0.27), 100	0.227	–0.05 (–0.13 to 0.04)
6 months	0.71 (0.22), 69	0.68 (0.26), 72	0.307	0.04 (–0.04 to 0.12)
VAS				
Randomisation	50 (22), 160	50 (22), 164	0.791	1 (–4 to 6)
1 months	59 (23), 132	55 (25), 132	0.238	4 (–2 to 9)
3 months	63 (23), 95	60 (23), 98	0.408	3 (–4 to 9)
6 months	66 (23), 70	66 (21.4), 71	0.980	0 (7 to 8)
SF-6D utility				
Randomisation	0.58 (0.11), 157	0.56 (0.12), 153	0.265	0.01 (–0.01 to 0.04)
1 months	0.59 (0.11), 125	0.60 (0.12), 123	0.782	0.00 (–0.03 to 0.03)
3 months	0.63 (0.11), 89	0.64 (0.14), 96	0.903	0.00 (–0.04 to 0.03)
6 months	0.65 (0.12), 67	0.64 (0.12), 71	0.769	0.01 (–0.03 to 0.05)

Resource use

Initial hospitalisation

We evaluated initial length of stay for both participant groups. This was calculated from date of admission (as opposed to date of randomisation) to date of discharge. We had missing data on dates of discharge or admission for two participants. For a further four participants, we had missing data on the specialty wards they had been admitted to, so we were be unable to obtain initial hospitalisation costs for these four participants. As a result, data were missing for six participants.

Participants randomised to thoracoscopy-delivered talc poudrage had an initial length of stay of 6.366 (SD 10.800, $n = 164$) days compared with 6.794 (SD 6.679, $n = 160$) days for participants randomised to standard chest tube talc slurry pleurodesis. This was a non-significant difference of 0.428 days (95% CI difference –1.540 to 2.396 days; $p = 0.669$).

Follow-up resource use

Information on 1-, 3- and 6-month resource use is presented in *Appendix 2*. *Table 28* presents the mean NHS resource-use estimates over the 6 months after randomisation, evaluated using available-case analysis. There were no statistically significant differences in NHS or hospice care resource-use consumption patterns between the two participant groups over the 6 months after randomisation.

Additional data regarding resource use may be found in *Appendix 2* (see *Tables 36* and *37*).

TABLE 28 Follow-up resource use up to 6 months

Type of resource use	Treatment arm, mean (95% CI)		Mean difference (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry	
General practice consultations			
Surgery	1.6 (1.3 to 1.8)	1.8 (1.4 to 2.1)	–0.2 (–0.6 to 0.2)
Home	0.7 (0.5 to 0.8)	0.6 (0.1 to 0.9)	0.1 (–0.3 to 0.3)
Telephone	1.0 (0.7 to 1.2)	0.8 (0.6 to 1.1)	0.2 (–0.2 to 0.5)
Outpatient visits	5.5 (4.7 to 6.2)	5.8 (5.2 to 6.6)	–0.3 (–1.4 to 0.6)
A&E visits	0.5 (0.4 to 0.6)	0.5 (0.4 to 0.6)	0.0 (–0.2 to 0.2)
Ambulance use	0.2 (0.1 to 0.3)	0.3 (0.2 to 0.4)	–0.1 (–0.2 to 0.1)
Hospitalisations	1.1 (0.9 to 1.2)	0.9 (0.8 to 1.1)	0.2 (–0.1 to 0.3)
Length of stay (days)	6.7 (5.4 to 8.0)	5.5 (4.3 to 6.8)	1.2 (–0.5 to 3.0)
Hospice care			
Length of stay (days)	1.5 (0.6 to 2.5)	1.1 (0.3 to 2.3)	0.4 (–1.1 to 1.6)
Hospice nurse visits	0.8 (0.2 to 1.8)	0.6 (0.4 to 0.9)	0.2 (–0.5 to 1.1)
Nurse consultations			
Clinic	2.3 (1.8 to 2.8)	2.9 (2.4 to 3.5)	–0.6 (–1.4 to 0.1)
Home	6.6 (4.1 to 9.3)	7.0 (4.9 to 9.1)	–0.4 (–3.9 to 3.0)
Physiotherapist visits	0.3 (0.1 to 0.5)	0.2 (0.1 to 0.3)	0.1 (–0.1 to 0.3)
Occupational therapist visits	0.2 (0.1 to 0.3)	0.2 (0.1 to 0.3)	0.0 (–0.1 to 0.2)
Psychologist visits	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.1)	0.0 (–0.1 to 0.1)
Counsellor visits	0.1 (0.0 to 0.2)	0.1 (0.0 to 0.2)	0.0 (–0.1 to 0.1)
Day hospital visits	1.3 (0.9 to 1.8)	2.0 (1.3 to 2.9)	–0.7 (–1.6 to 0.2)

Costs

Procedure costs

Table 29 details the per-patient costs of performing each of the two trial interventions. On average, for the procedures observed, participants randomised to standard chest tube talc slurry pleurodesis remained in theatre for 31 minutes while the drain was inserted. In addition, these participants required an additional 30 minutes for talc installation, but this was not undertaken in theatre. Participants randomised to thoracoscopy-delivered talc poudrage remained in theatre for 70 minutes. Per-patient costs of thoracoscopy-delivered talc poudrage were £1273, compared with £753 for standard chest tube talc slurry pleurodesis.

Overall costs

Information on costs accrued by participants at the 1-, 3- and 6-month follow-ups are reported in *Appendix 2*. *Table 30* presents mean total NHS and hospice care costs over the 6 months after randomisation, evaluated using available-case analysis. As shown, there were no statistically significant differences in NHS or hospice care costs between the two participant groups over the 6 months after randomisation.

Over 6 months, participants randomised to thoracoscopy-delivered talc poudrage incurred mean costs of £10,687 (95% CI £9621 to £11,627) per participant compared with £10,146 (95% CI £9119 to £11,212) for participants randomised to standard chest tube talc slurry pleurodesis. As a result, participants randomised to thoracoscopy-delivered talc poudrage incurred additional costs of £541, over 6 months, compared with participants randomised to standard chest tube talc slurry pleurodesis, an increase that was not found to be significant (95% CI difference –£9533 to £1933).

Further data regarding costs may be found in *Appendix 2* (see *Tables 38* and *39*).

Cost-effectiveness

Mean QALY gain was 0.239 in the standard chest tube talc slurry pleurodesis group and 0.246 in the thoracoscopy-delivered talc poudrage group, a mean difference of 0.007 (95% CI –0.019 to 0.034) (*Table 31*).

TABLE 29 Calculated per-patient costs for each procedure

	Treatment arm, cost (£)	
Reason for cost	Thoracoscopy and poudrage	Chest drain and slurry
Theatre usage	407	158
Medical staff	545	290
Equipment for thoracoscopy	42	0
Disposables	52	80
Medication and sedation	9	7
Investigation	218	218
Total cost	1273	753

TABLE 30 Mean NHS costs at 6 months

Type of resource use	Treatment arm, mean cost (£) (95% CI)		Mean difference (£) (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry	
Initial hospitalisation	2796 (2298 to 3374)	2901 (2534 to 3309)	–105 (–928 to 718)
Intervention costs	1273 (N/A)	753 (N/A)	520 (N/A)
General practice consultations			
Surgery	57 (47 to 66)	63 (52 to 76)	–6 (–23 to 7)
Home	60 (43 to 79)	56 (38 to 78)	4 (–24 to 31)
Telephone	27 (20 to 34)	23 (17 to 30)	4 (–6 to 14)
Outpatient visits	684 (593 to 774)	736 (650 to 824)	–52 (–175 to 70)
A&E visits	70 (54 to 86)	71 (55 to 88)	–1 (–24 to 21)
Ambulance use	44 (31 to 60)	57 (40 to 76)	–13 (–37 to 10)
Follow-up hospitalisations	3657 (2906 to 4397)	3124 (2459 to 3870)	533 (–478 to 1569)
Hospice care			
Hospice admissions	578 (231 to 979)	436 (117 to 898)	142 (–428 to 649)
Hospice nurse visits	92 (26 to 199)	69 (42 to 98)	23 (–55 to 125)
Nurse consultations			
Clinic	32 (26 to 40)	41 (34 to 49)	–9 (–20 to 1)
Home	269 (166 to 382)	286 (200 to 372)	–17 (–158 to 121)
Physiotherapist visits	14 (7 to 24)	11 (6 to 17)	3 (–6 to 14)
Occupational therapist visits	15 (9 to 23)	15 (7 to 23)	0 (–10 to 11)
Psychologist visits	10 (0 to 25)	10 (2 to 21)	0 (–15 to 16)
Counsellor visits	17 (3 to 32)	17 (5 to 31)	0 (–20 to 19)
Day hospital visits	988 (685 to 1336)	1475 (961 to 2113)	–487 (–1207 to 156)
Total costs	10,687 (9621 to 11,627)	10,146 (9119 to 11,212)	541 (–953 to 1933)

N/A, not applicable.

TABLE 31 Cost-effectiveness

Summary measure	Treatment arm, mean (95% CI)		Mean difference (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry	
Total costs (£)	10,687 (9621 to 11,627)	10,146 (9119 to 11,212)	541 (–953 to 1933)
Total QALYs	0.246 (0.227 to 0.263)	0.239 (0.217 to 0.258)	0.007 (–0.019 to 0.034)
ICER (£)			77,286
Probability talc poudrage is cost-effective			
£20,000 threshold			0.36
£50,000 threshold			0.45

Therefore, the incremental cost per QALY gained when thoracoscopy-delivered talc poudrage was compared with standard chest tube talc slurry pleurodesis was £77,286. At the conventional £20,000 per QALY gained threshold, thoracoscopy-delivered talc poudrage would have a 0.36 probability of being cost-effective (*Figure 10*). The cost-effectiveness plane shows that, of the 1000 simulations, 36% fall below the £20,000 per QALY willingness-to-pay threshold. If we apply the NICE end-of-life criteria, with the willingness-to-pay threshold rising to £50,000 per QALY, the probability that thoracoscopy-delivered talc poudrage is cost-effective rises to 0.45, with this probability rising to 0.54 at a willingness-to-pay threshold of £100,000 per QALY gained (*Figure 11*).

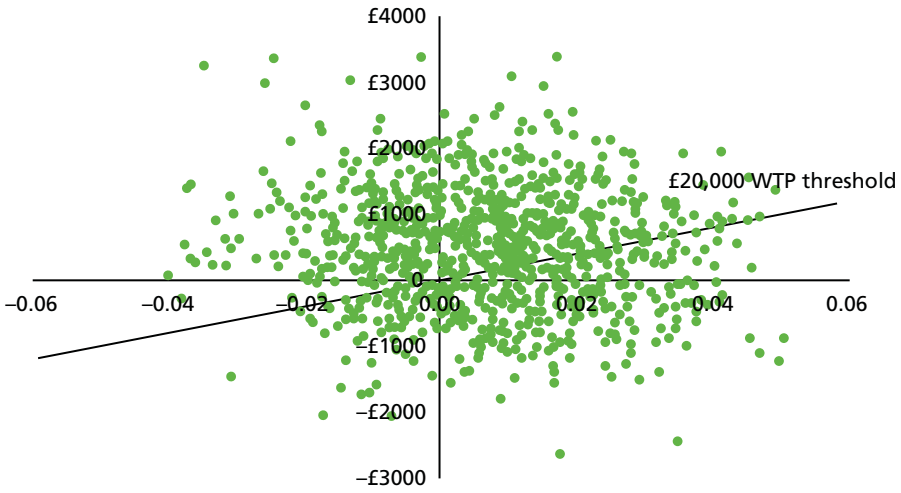

FIGURE 10 Cost-effectiveness plane. WTP, willingness to pay.

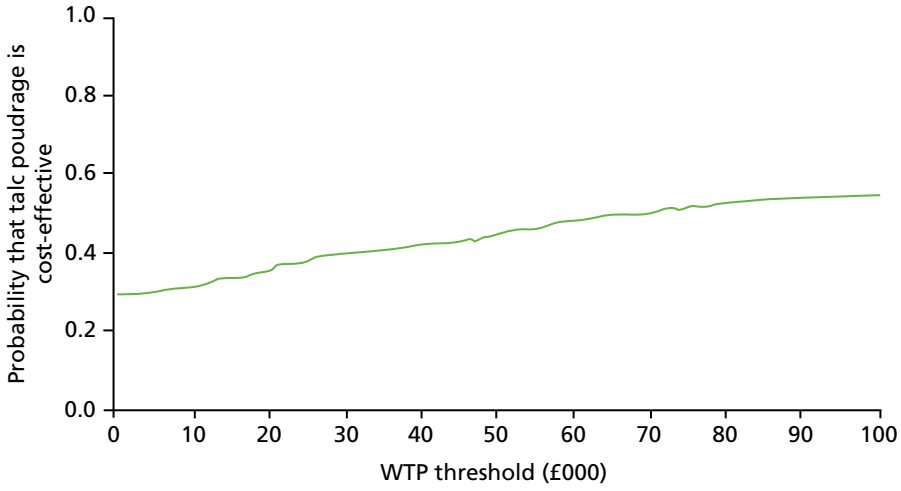

FIGURE 11 Cost-effectiveness acceptability curve. WTP, willingness to pay.

Sensitivity analysis

When the time to perform thoracoscopy-delivered talc poudrage was reduced from 70 to 60 minutes, the costs of the intervention fell from £1273 to £1137. As a result, mean total NHS and hospice care costs at 6 months for participants randomised to thoracoscopy-delivered talc poudrage reduced to £10,513 (95% CI £9485 to £11,495). Therefore, the mean cost difference between participants randomised to thoracoscopy-delivered talc poudrage and those participants randomised to standard chest tube talc slurry pleurodesis was £346 (95% CI difference –£1089 to £1798). This resulted in an incremental cost per QALY gained of £49,429, when thoracoscopy-delivered talc poudrage was compared with standard chest tube talc slurry pleurodesis. At the conventional £20,000 per QALY gained threshold, thoracoscopy-delivered talc poudrage would have a 0.41 probability of being cost-effective. Using NICE's end-of-life criteria (i.e. a threshold of £50,000 per QALY gained), the probability that thoracoscopy-delivered talc poudrage is cost-effective would be 0.50.

Multiple imputation of missing data

After multiple imputation of missing EQ-5D-5L utility values, average utilities at each follow-up were found to be lower than in the complete-case analysis (*Table 32*). As in the available-case analysis, differences in utility also remained non-significant between the two treatment groups. However, at the 3- and 6-month follow-up, mean differences between groups varied between the available-case analysis and the multiple imputation analysis (–0.05 vs. –0.07 at 3 months, respectively, and 0.04 vs. 0.02 at 6 months, respectively).

After survival data were combined with EQ-5D-5L utilities obtained in the multiple imputation analysis, the difference in QALYs gained when thoracoscopy-delivered talc poudrage was compared with standard chest tube talc slurry pleurodesis was 0.00007 (i.e. 0.22336 QALYs for thoracoscopy and 0.22328 QALYs for standard chest).

After multiple imputation, we found that thoracoscopy-delivered talc poudrage was £361 (95% CI difference –£1257 to £1979) more costly than standard chest tube talc slurry pleurodesis per patient (*Table 33*). This difference was smaller than the £541 (95% CI difference –£953 to £1933) difference observed in the available-case analysis.

As the multiple imputation analysis results showed virtually no difference in QALYs gained between the two treatment groups, the incremental cost per QALY gained when thoracoscopy-delivered talc poudrage was compared with standard chest tube talc slurry pleurodesis was in excess of £4M in the multiple imputation analysis.

TABLE 32 The EQ-5D-5L utility after multiple imputation of missing cases

Time point	Treatment arm, mean (SD), *n*		$p > \|z\|$	Mean difference (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry		
Randomisation	0.57 (0.25), 166	0.55 (0.26), 164	0.571	0.02 (–0.04 to 0.07)
1 month	0.58 (0.27), 156	0.58 (0.28), 150	0.670	0.01 (–0.06 to 0.07)
3 months	0.53 (0.32), 131	0.60 (0.31), 122	0.563	–0.07 (–0.13 to 0.04)
6 months	0.60 (0.33), 102	0.59 (0.33), 98	0.728	0.02 (–0.06 to 0.12)

TABLE 33 Mean NHS costs at 6 months after multiple imputation of missing cases

Reason for cost	Treatment arm, mean (£)		Mean cost (£) difference (95% CI)
	Thoracoscopy and poudrage	Chest drain and slurry	
Initial hospitalisation	2792	2902	–111 (–925 to 703)
Intervention costs	1273	753	520 (N/A)
General practice consultations	145	140	5 (–37 to 47)
Follow-up hospitalisation costs	4868	4971	–103 (–1510 to 1340)
Hospice and nursing care	480	427	53 (–206 to 311)
Other health-care costs	48	51	–2 (–37 to 32)
Total costs	9606	9245	361 (–1257 to 1979)

N/A, not applicable.

Chapter 6 Discussion and conclusions

Summary of main trial findings

The TAPPS trial achieved its recruitment target of 330 participants. The results appear to be conclusive, in that there was no evidence of any difference between the two treatment arms in the primary outcome measure, pleurodesis failure at 90 days post randomisation. Indeed, there was no suggestion of a difference in any of the secondary outcome measures, including pleurodesis failure up to the final follow-up visit at 180 days post randomisation, mortality, time spent in hospital, radiological appearances or patient-reported outcomes. Sensitivity analyses supported the findings for the primary outcome, and it is improbable that missing data led to a significant effect.

Absolute values for pleurodesis failure were low (approximately 23% in both arms) at 90 days. Previous literature has suggested 30-day failure rates of approximately 10% for poudrage, which is in line with our findings.[5,25] Interestingly, we also saw a similarly low rate of failure in those participants treated with slurry. This is at odds with previous reports[25] and may be because our trial took place in clinical environments where there are more varied treatment options, including IPCs, meaning that those participants being considered for inpatient pleurodesis may be a subtly different population to those participants included in earlier studies.

Prespecified subgroup analyses did not reveal any differences in treatment effect by baseline performance status or underlying malignancy type. A significant interaction was noted for participants on steroids at baseline; however, participants numbers for this analysis were small. Estimated treatment effects were different between those participants on anticancer treatment at baseline and those participants not on anticancer treatment (OR 1.96 vs. 0.65), although the interaction was not statistically significant ($p = 0.08$) and, once again, participant numbers in this subgroup were small.

Approximately 50% of participants in the trial experienced an AE during their participation, with half of these experiencing an event that was classified as serious (including death). The majority of events were unrelated to the trial interventions, typically being associated with progression of the underlying malignancy. No difference in the numbers, or timings, of AEs or SAEs was noted between the treatment groups.

Summary of health economic findings

The results of the economic evaluation of the TAPPS trial are in line with those results of the effectiveness analysis, in that there is no clear evidence suggesting that either of the two interventions is superior in terms of costs or quality-adjusted life expectancy. However, the incremental cost-effectiveness analysis suggests that LAT and talc poudrage was not cost-effective when compared with talc slurry pleurodesis at current standard NICE thresholds of cost-effectiveness (£20,000 per QALY gained), with a likelihood of 0.36 of poudrage being superior. Applying a higher threshold of £50,000 per QALY gained (which has been suggested by NICE for patients who are in the palliative stages of treatment) increases the probability that poudrage is cost-effective (to 0.45), but the overall likelihood remains less probable than slurry being the more cost-effective method.

There are, however, limitations to the above. Primarily due to patients dying in between follow-ups and, to a lesser degree, withdrawing from the trial, there were missing data, particularly with regard to follow-up costs. We tried to minimise missing resource-use data by asking clinical staff to complete some of the questions, including those patients asking about ambulance and A&E use, outpatient visits and hospitalisations, through review of patients' hospital records. As a result, rather than reduce our sample size even further by restricting our analysis to patients with complete-case information (i.e. had to have information on all resource-use items and quality-of-life estimates), we used an available-case analysis to determine mean costs and quality-of-life

estimates. In addition to this, we also performed a sensitivity analysis using multiple imputation methods. This analysis also confirmed that thoracoscopy-delivered talc poudrage is unlikely to be cost-effective, as the ICER after this analysis was in excess of £4M.

Trial strengths

The trial was conducted and reported in line with CONSORT recommendations. To the best of our knowledge, the TAPPS trial is the first RCT to examine the efficacy of talc poudrage delivered at LAT compared with traditional talc slurry. It addresses a clear and important area of uncertainty in clinical practice and has been able to inform this in a robust manner. The trial processes, including randomisation and treatment allocations, were robustly designed, with the likelihood of bias minimised as far as possible, and the trial interventions were performed in a standardised fashion that is reflective of current practice, meaning that the results are likely to be generalisable to the wider population.

The two treatment groups were well matched at baseline, with a distribution of malignancies in line with previous data. Retention to follow-up was high; thus, the trial was suitably powered to address the primary research question. The primary outcome was assessed at a time point of significant relevance to both patients and carers, with its definition robust, pragmatic and clinically meaningful to modern UK practice. The analysis took place using the intention-to-treat principle and followed a prespecified plan that was assessed and approved by the TSC. We performed a comprehensive sensitivity analysis, which supports the primary outcome finding, and ensured that any potentially controversial decisions relating to reporting the primary outcome were assessed in a blinded fashion. The secondary outcomes and subgroup analyses were chosen to examine both previous studies' findings and important supplementary clinical questions.

We also performed a comprehensive health economic analysis – the first of its kind in the trial population and interventions under investigation. This analysis was performed from the perspective of the NHS and so, as for the effectiveness analysis, the results are likely to be able to inform current UK practice.

Trial limitations

The trial entry criteria specified that patients be sufficiently fit to undergo LAT under light sedation, which may reduce the degree of generalisability of the results to those patients presenting with a greater degree of frailty (who do not wish to undergo IPC insertion).

The trial was conducted on an open-label basis, as it was not deemed feasible or ethical to blind participants and/or perform sham procedures, which may have influenced the results of patient-reported measures, such as pain or breathlessness. In additional, due to the organisation of most recruiting centres, it is probable that those clinicians responsible for the recruitment and trial interventions were also required to assess participants for pleurodesis failure, introducing the potential for bias (although this was considered and addressed through blinded reassessment, as above).

The duration of follow-up was limited to 6 months. For participants with a certain malignancy, such as mesothelioma or breast cancer, this may not have been long enough a period to fully inform care over the duration of what may be a longer average survival period. The follow-up period may also have had an impact on the health economic evaluation, as it did not encompass the whole remaining life of the participant, meaning longer-term projections regarding costs cannot be made. However, at 6 months, > 65% of the trial participants had died and prognosis for 6-month survivors was poor. As a result, we believe that the main impact of the interventions under study, both in terms of costs and outcomes, were captured.

Recruitment challenges

Although the trial achieved its target, this was only possible as a result of an extension in the recruitment period and site numbers to accommodate lower than expected accrual, the original predicted requirements being 3 years and eight centres, respectively. During the course of the trial, close liaison with PIs and scrutiny of screening logs revealed a range of potential reasons for this disparity. These included:

- Patients declining enrolment, largely influenced by the significant comorbidities and degree of symptoms that most MPE patients experience, but also by preconceptions of research and previous clinical encounters.
- Patients favouring one treatment arm over the other after reading trial information, and thus declining randomisation. This effect did not appear to favour either treatment arm, with the patient information sheet carefully written to express equipoise, suggesting individual patient preference was key.
- Patients favouring IPC to pleurodesis approach. As an increasing number of centres became able, and willing, to offer IPCs to patients during the trial period (an effect which could not have been predicted at the time of the original grant application), it was, perhaps, inevitable that some patients who historically could not have been offered a treatment choice would elect to have an IPC placed over a talc pleurodesis.
- Patients being admitted and managed for the MPE acutely, thereby missing recruitment windows. This appeared to be an issue that varied according to the pre-established referral and patient discovery pathways at individual sites, with the effect being compounded if there was a lack of pleural-specific personnel on site.
- Patients needing a tissue diagnosis. This appeared to be the most common reason for patients not being enrolled into the TAPPS trial and was, perhaps, the most predictable. Given that the vast majority of medical thoracoscopy is undertaken for the diagnosis of first-presentation pleural effusions, it was always expected that the numbers of patients who would be enrolled to the trial, for purely therapeutic treatment, would be relatively low. There also appeared to be an increasing trend in certain centres for oncology colleagues to request thoracoscopic biopsies for all those patients with an effusion, regardless of established diagnosis, to facilitate novel tumour marker discovery, which may, theoretically, alter treatment. This practice meant that some of those patients, who traditionally would have needed only a pleurodesis and, hence, would be eligible for trial inclusion, had to be excluded on the grounds that they could not ethically be randomised to chest drain and slurry.

Patient and public involvement

Patient and public involvement in the TAPPS trial occurred in two distinct phases.

First, the main trial protocol, patient information sheets and consent forms were developed and approved with input from the lay members of the TSC, both of whom were relatives of patients who had suffered with MPE.

Second, these members remained a key part of the ongoing trial management, participating in all TSC meetings and contributing from a non-medical perspective to ensure that the trial maintained its priorities of being patient focused and pragmatic. In addition, during the course of the trial, a non-specialist summary was prepared in conjunction with medical writers at Cancer Research UK. This summary was made publicly available and ensured that the trial questions and aims were sufficiently approachable for a general audience.

Conclusions: interpretation of results

The results of the primary analysis have robustly demonstrated that there is no additional benefit in performing talc poudrage at LAT over bedside chest drain and talc slurry for the management of MPE.

This finding is in line with that noted in the Dresler *et al.* study,[25] although, in contrast, we were unable to demonstrate any signal for greater effectiveness of poudrage in any particular malignant subgroup. In additional, no differences were found to suggest that there are advantages to either treatment with regard to time spent in hospital or procedural safety.

When applying a standard NICE treatment threshold of £20,000 per QALY gained, the results of the economic evaluation of the TAPPS trial would suggest that poudrage at LAT is unlikely to be a cost-effective way to deliver talc. Applying the higher £50,000 threshold suggested that for palliative patients (which is likely to be the best descriptor of the patients included in this trial), poudrage remains less likely to be cost-effective, but by a much smaller margin.

Overall, the TAPPS trial has been unable to demonstrate any evidence to support choosing talc poudrage over talc slurry for inducing a pleurodesis in patients with MPEs.

Future research and the management pathway for malignant pleural effusion

Despite the rise of newer approaches to the management of MPE in the UK, talc pleurodesis – and in particular inpatient talc pleurodesis as studied in the TAPPS trial – remains an important option for what is likely to be the majority of patients. When considering the wider context, beyond the NHS, safe outpatient management of MPE is not, as yet, achievable in most health-care environments, making these results all the more pertinent.

In the UK, it is now widely accepted that patients be offered the choice of how they wish their MPE to be managed: either as an outpatient with an IPC or as an inpatient with an attempt at talc pleurodesis, although it must be noted that, to the best of our knowledge, there have not been any trials comparing inpatient and outpatient methods powered to examine pleurodesis success as the primary outcome. For those patients choosing an inpatient approach (i.e. an explicit attempt at preventing further fluid), the TAPPS trial would not support choosing medical thoracoscopy and poudrage over traditional talc slurry. There may be, however, other reasons to perform a thoracoscopy, including the acquisition of further tissue for targeted anticancer therapy.

There remain a number of important research questions relating to the 'best' way to manage patients presenting with symptomatic MPE. Treatment combinations and hybrid pathways are increasingly being considered, allowing for greater personalisation and adaptation to a patient's needs. RCTs, potentially multiarm, that incorporate the use of an IPC alone, an IPC in combination with talc slurry or an IPC placed at the time of a diagnostic thoracoscopy (for example), and that compare these treatments to 'traditional' approaches, may be informative. To complement any such study, it would be vital to gather comprehensive health economic data to clarify which treatments are likely to be cost-effective. Indeed, for understanding costs, a prospective observational design may be sufficient and would also allow the possibility of examining less-used, locally bespoke pathways or those patients who choose to undergo non-definitive treatments, such as repeat thoracentesis.

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Trial registration and ethics approval

The TAPPS trial was given initial ethics approval by the National Research Ethics Service Committee (North West – Preston) on 26 June 2012. The ethics approval number was 12/NW/0467. All subsequent substantial amendments were reviewed and approved by the same committee.

The TAPPS trial was registered on the publicly accessible ISRCTN database prior to recruitment beginning (ISRCTN47845793).[30]

Contributions of authors

Rahul Bhatnagar was trial co-ordinator, assisted with data collection and analysis, and was primary contributor to the report manuscript.

Ramon Luengo-Fernandez performed the health economic evaluation and contributed to the report manuscript.

Brennan C Kahan performed all other data analyses and contributed to the report manuscript.

Najib M Rahman was a key trial investigator, led trial management team in Oxford and contributed to the report manuscript.

Robert F Miller was chairperson of the TSC and contributed to the report manuscript.

Nick A Maskell was trial chief investigator and takes overall responsibility for the contents of the report manuscript.

All authors have approved the final draft of the manuscript after reviewing its contents.

Publications

Bhatnagar R, Laskawiec-Szkonter M, Piotrowska HE, Kahan BC, Hooper CE, Davies HE, *et al.* Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. *BMJ Open* 2014;**4**:3007045.

Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, Kahan BC, Luengo-Fernandez R, Pepperell JCT, *et al.* Effect of thoracoscopic talc poudrage vs talc slurry via chest tube on pleurodesis failure rate among patients with malignant pleural effusions: a randomized clinical trial. *JAMA* 2020;**323**:60–69.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to available anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 The TAPPS trial standard operating procedures for talc slurry and talc poudrage

Trial-specific procedure for drain insertion (control arm)

Drain insertion

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

Drainage plan

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

Trial-specific procedure for slurry instillation (control arm)

Talc slurry pleurodesis

- Procedure may be performed at the patient's bedside as long as aseptic technique is maintained.
- Explain procedure.
- Administer premedication (e.g. 10 mg of oral morphine solution).
- Position the patient comfortably, allowing access to the drain.
- Expose the three-way tap.
- Clean the access port using an alcohol-based swab.
- Instil 10 ml of sterile 0.9% saline into the pleural cavity via the three-way tap to ensure drain patency.
- Instil 3 mg/kg (maximum 250 mg) of 1% lidocaine hydrochloride in to the pleural space via the three-way tap.
- Turn the tap off to the drain (clamp) for 10 minutes.

- Make up 4 g of sterile talc to a slurry using 50 ml of 0.9% sterile saline.
- Instil the slurry in to the pleural cavity via the three-way tap at least 10 minutes after lidocaine hydrochloride instillation.
- Flush 20 ml of 0.9% saline into the pleural cavity via the three-way tap.
- Turn the tap off to the drain (clamp) for 2 hours.
- Re-open the three-way tap to both the drain and the drainage bottle.
- Apply thoracic suction (–10 to –20 cm water) for at least 24 hours.
- Ensure that the patient is prescribed adequate analgesia.
- 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.
- A CXR should be performed between 18 and 24 hours post talc instillation.

Post pleurodesis

- Drains should remain in place for at least 24 hours post talc slurry instillation.
- Drainage volumes should continue to be recorded at least every 8 hours.
- Once drainage volumes fall below 250 ml in the preceding 24 hours, the drain may be removed.
- A posterior–anterior CXR should be performed prior to the patient being discharged home.

Trial-specific procedure for medical thoracoscopy (intervention arm)

Thoracoscopy and poudrage

- Procedure ideally to be performed in dedicated theatre, endoscopy suite or 'clean environment' (e.g. dedicated procedure room).
- Explain procedure.
- Obtain written consent for medical thoracoscopy.
- Position patient and administer sedation as necessary.
- Perform thoracic ultrasonography to confirm safe site for port insertion.
- Prepare kit, including filling drainage bottle to pre-marked prime line.
- Don sterile gown and gloves and sterilise insertion site using appropriate skin preparation.
- Infiltrate local anaesthetic to skin and down to pleura.
- Make adequate skin incision.
- A closing suture should be placed either at this point or towards the end of the procedure.
- Create port site by dissecting down to pleura.
- Insert trocar and port before removing trocar to leave port in situ.
- Aspirate chest cavity to dryness using flexible suction catheter. Record total drainage volume.
- 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.
- At the end of the procedure spray 4 g of sterile talc over the pleural surface using a poudrage kit, aiming for an even spread of talc. Ensure that there is enough space left around the delivery tube/needle to allow air to escape (to avoid inducing a tension pneumothorax).
- Remove the thoracoscopy port and insert a 16–24 French chest drain via the port tract.
- Secure drain in place and apply appropriate dressings.
- Consider attaching a chest drain adaptor [e.g. Thal-Quick Chest Tube Adaptor (Cook Medical; Bloomington, IN, USA)] to allow easy pleural access without disconnecting the drain.
- Attach to an underwater drainage bottle using sterile tubing.
- Admit to ward and ensure adequate analgesia is prescribed.
- Connect to thoracic suction for at least 24 hours.
- A CXR should be performed to ensure adequate drain positioning.
- The drain should stay in place for at least 24 hours post poudrage.

Post thoracoscopy

- 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.
- A CXR should be performed between 18 and 24 hours post poudrage.
- Drainage volumes should be recorded at least every 8 hours.
- Once drainage volumes fall below 250 ml in the preceding 24 hours, the drain may be removed.
- A PA CXR should be performed prior to the patient being discharged home.

Appendix 2 Additional information relating to health economic analyses

TABLE 34 Quality of life: EQ-5D-5L responses

	Time point, *n* (%)			
EQ-5D-5L domain	Randomisation	1 month	3 months	6 months
Drain insertion and talc slurry				
Mobility				
No problems in walking about	37 (23)	38 (29)	33 (33)	23 (32)
Slight problems in walking about	37 (23)	23 (17)	20 (20)	20 (28)
Moderate problems in walking about	54 (33)	45 (34)	25 (25)	20 (28)
Severe problems in walking about	32 (20)	22 (17)	20 (20)	7 (10)
Unable to walk about	4 (2)	4 (3)	2 (2)	2 (3)
Self-care				
No problems washing or dressing	96 (59)	74 (56)	67 (67)	53 (74)
Slight problems washing or dressing	32 (20)	23 (17)	12 (12)	9 (13)
Moderate problems washing or dressing	23 (14)	23 (17)	16 (16)	5 (7)
Severe problems washing or dressing	9 (5)	8 (6)	2 (2)	4 (6)
Unable to wash or dress	4 (2)	4 (3)	3 (3)	1 (1)
Usual activities				
No problems doing usual activities	20 (12)	29 (22)	30 (30)	25 (35)
Slight problems doing usual activities	41 (25)	28 (21)	15 (15)	18 (25)
Moderate problems doing usual activities	42 (26)	33 (25)	29 (29)	16 (22)
Severe problems doing usual activities	39 (24)	19 (14)	13 (13)	10 (14)
Unable to do usual activities	22 (13)	23 (17)	13 (13)	3 (4)
Pain/discomfort				
No pain or discomfort	44 (27)	42 (32)	40 (40)	23 (32)
Slight pain or discomfort	49 (30)	49 (37)	25 (25)	30 (42)
Moderate pain or discomfort	46 (28)	34 (26)	29 (29)	14 (19)
Severe pain or discomfort	22 (13)	7 (5)	6 (6)	3 (4)
Extreme pain or discomfort	3 (2)	0 (0)	0 (0)	2 (3)
Anxiety/depression				
Not anxious or depressed	68 (41)	59 (45)	47 (47)	44 (61)
Slightly anxious or depressed	48 (29)	37 (28)	34 (34)	18 (25)
Moderately anxious or depressed	37 (23)	31 (23)	14 (14)	7 (10)
Severely anxious or depressed	9 (5)	5 (4)	5 (5)	2 (3)
Extremely anxious or depressed	2 (1)	0 (0)	0 (0)	1 (1)

continued

TABLE 34 Quality of life: EQ-5D-5L responses (*continued*)

EQ-5D-5L domain	Time point, *n* (%)			
	Randomisation	1 month	3 months	6 months
Thoracoscopy and talc poudrage				
Mobility				
No problems in walking about	34 (21)	32 (24)	27 (28)	26 (37)
Slight problems in walking about	44 (27)	40 (30)	29 (31)	23 (33)
Moderate problems in walking about	48 (29)	37 (28)	20 (21)	15 (21)
Severe problems in walking about	34 (21)	23 (17)	15 (16)	5 (7)
Unable to walk about	3 (2)	1 (1)	4 (4)	1 (1)
Self-care				
No problems washing or dressing	98 (60)	85 (64)	59 (62)	48 (69)
Slight problems washing or dressing	36 (22)	26 (20)	17 (18)	18 (26)
Moderate problems washing or dressing	22 (14)	16 (12)	12 (13)	3 (4)
Severe problems washing or dressing	6 (4)	3 (2)	4 (4)	0 (0)
Unable to wash or dress	1 (1)	3 (2)	3 (3)	1 (1)
Usual activities				
No problems doing usual activities	23 (14)	26 (20)	21 (22)	23 (33)
Slight problems doing usual activities	42 (26)	38 (29)	28 (29)	20 (29)
Moderate problems doing usual activities	47 (29)	29 (22)	18 (19)	20 (29)
Severe problems doing usual activities	31 (19)	21 (16)	16 (17)	5 (7)
Unable to do usual activities	20 (12)	19 (14)	12 (13)	2 (3)
Pain/discomfort				
No pain or discomfort	32 (20)	37 (28)	29 (30)	28 (40)
Slight pain or discomfort	64 (39)	52 (40)	33 (35)	28 (40)
Moderate pain or discomfort	46 (28)	29 (22)	25 (26)	13 (19)
Severe pain or discomfort	18 (11)	14 (11)	7 (7)	1 (1)
Extreme pain or discomfort	3 (2)	0 (0)	1 (1)	0 (0)
Anxiety/depression				
Not anxious or depressed	70 (43)	58 (44)	43 (45)	36 (52)
Slightly anxious or depressed	55 (34)	48 (36)	24 (25)	20 (29)
Moderately anxious or depressed	24 (15)	18 (14)	22 (23)	11 (16)
Severely anxious or depressed	12 (7)	6 (5)	4 (4)	1 (1)
Extremely anxious or depressed	2 (1)	3 (2)	2 (2)	1 (1)

TABLE 35 The SF-36 responses

	Treatment arm				
	Chest drain and slurry		Thoracoscopy and poudrage		
Domain and time point	*n*	Mean (SD)	*n*	Mean (SD)	$p > \|z\|$
Randomisation					
Physical functioning	159	30 (25)	163	33 (29)	0.329
Role physical	163	24 (24)	164	28 (27)	0.230
Role emotional	162	53 (38)	163	54 (34)	0.761
Social functioning	163	38 (31)	162	41 (29)	0.514
Mental health	157	61 (23)	160	64 (21)	0.377
Energy/vitality	158	30 (22)	161	31 (23)	0.970
Pain	164	52 (31)	164	51 (30)	0.968
General health perception	161	40 (23)	161	41 (21)	0.501
Mental component score	142	50 (26)	148	51 (23)	0.699
Physical component score	142	26 (23)	148	27 (24)	0.556
1 month					
Physical functioning	128	38 (28)	127	37 (27)	0.717
Role physical	132	30 (30)	131	32 (29)	0.503
Role emotional	131	59(35)	130	60 (36)	0.826
Social functioning	128	48 (33)	128	47 (30)	0.712
Mental health	129	65 (23)	129	65 (22)	0.910
Energy/vitality	131	34 (23)	130	34 (22)	0.886
Pain	132	60 (28)	131	55 (28)	0.167
General health perception	129	37 (21)	130	38 (20)	0.789
Mental component score	119	54 (25)	119	55 (24)	0.856
Physical component score	119	32 (25)	119	29 (26)	0.435
3 months					
Physical functioning	97	44 (30)	93	40 (29)	0.335
Role physical	97	40 (34)	96	38 (29)	0.712
Role emotional	97	66 (35)	93	65 (35)	0.912
Social functioning	99	57 (33)	91	55 (31)	0.716
Mental health	98	69 (22)	91	68 (21)	0.634
Energy/vitality	99	42 (23)	93	41 (23)	0.634
Pain	99	63 (30)	94	65 (27)	0.600
General health perception	97	39 (21)	93	39 (23)	0.964
Mental component score	93	61 (24)	85	58 (25)	0.524
Physical component score	93	38 (29)	85	36 (25)	0.739

continued

TABLE 35 The SF-36 responses (*continued*)

Domain and time point	Treatment arm: Chest drain and slurry *n*	Chest drain and slurry Mean (SD)	Thoracoscopy and poudrage *n*	Thoracoscopy and poudrage Mean (SD)	$p > \|z\|$
6 months					
Physical functioning	69	50 (29)	68	50 (27)	0.951
Role physical	72	48 (31)	69	49 (28)	0.830
Role emotional	72	71 (30)	69	70 (32)	0.863
Social functioning	72	60 (32)	70	65 (27)	0.263
Mental health	71	73 (21)	69	72 (20)	0.729
Energy/vitality	72	43 (25)	69	46 (23)	0.451
Pain	72	67 (29)	69	66 (28)	0.764
General health perception	72	41 (21)	69	42 (26)	0.731
Mental component score	68	62 (23)	64	64 (22)	0.650
Physical component score	68	41 (26)	64	43 (28)	0.684

TABLE 36 Resource use at each follow-up: drain insertion and talc slurry

Type of resource use	Time point, mean (SD), *n*: 1 month	3 months	6 months
General practice consultations			
Surgery	0.39 (0.65), 133	0.62 (1.17), 121	0.76 (1.48), 125
Home	0.17 (0.72), 134	0.20 (0.79), 122	0.25 (0.83), 123
Telephone	0.22 (0.69), 134	0.39 (0.99), 119	0.21 (0.71), 121
Outpatient visits	1.38 (1.52), 146	2.24 (2.43), 140	2.26 (3.01), 142
A&E visits	0.12 (0.37), 147	0.20 (0.51), 143	0.19 (0.53), 142
Ambulance use	0.06 (0.24), 144	0.12 (0.37), 138	0.09 (0.37), 138
Length of stay (days)	1.58 (3.79), 148	2.13 (5.12), 143	1.80 (4.58), 138
Hospice care			
Length of stay (days)	0.01 (0.08), 139	0.10 (0.65), 133	0.99 (7.07), 130
Hospice nurse visits	0.18 (0.69), 138	0.25 (1.02), 127	0.18 (0.84), 125
Nurse consultations			
Clinic	0.83 (1.27), 140	1.16 (1.87), 130	0.95 (2.10), 127
Home	0.72 (2.31), 137	3.19 (8.83), 124	3.08 (7.78), 120
Physiotherapist visits	0.10 (0.53), 139	0.06 (0.39), 125	0.06 (0.39), 124
Occupational therapist visits	0.06 (0.31), 138	0.09 (0.55), 125	0.07 (0.33), 122
Psychologist visits	0.03 (0.17), 139	0.02 (0.27), 125	0.02 (0.18), 124
Counsellor visits	0.01 (0.12), 138	0.62 (1.17), 121	0.76 (1.48), 125
Day hospital visits	0.28 (0.99), 138	0.20 (0.79), 122	0.25 (0.83), 123

TABLE 37 Resource use at each follow-up: thoracoscopy and talc poudrage

	Time point, mean (SD), *n*		
Type of resource use	1 month	3 months	6 months
General practice consultations			
Surgery	0.35 (0.61), 142	0.69 (1.03), 116	0.54 (0.99), 110
Home	0.17 (0.49), 141	0.21 (0.62), 114	0.28 (0.84), 110
Telephone	0.19 (0.56), 141	0.35 (0.80), 115	0.42 (1.17), 109
Outpatient visits	1.21 (1.45), 152	2.03 (2.28), 144	2.24 (2.99), 101
A&E visits	0.15 (0.41), 152	0.19 (0.50), 144	0.17 (0.45), 133
Ambulance use	0.08 (0.32), 152	0.06 (0.23), 141	0.08 (0.32), 131
Length of stay (days)	2.05 (4.72), 151	3.17 (7.06), 144	1.50 (3.83), 137
Hospice care			
Length of stay (days)	0.13 (1.05), 145	0.55 (3.02), 132	0.78 (4.14), 121
Hospice nurse visits	0.09 (0.42), 144	0.63 (5.45), 126	0.11 (0.65), 114
Nurse consultations			
Clinic	0.54 (0.93), 145	0.79 (1.38), 129	0.96 (2.10), 89
Home	0.94 (3.20), 143	2.95 (9.95), 120	3.84 (12.42), 124
Physiotherapist visits	0.04 (0.23), 146	0.09 (0.40), 127	0.17 (0.88), 121
Occupational therapist visits	0.07 (0.37), 145	0.09 (0.44), 127	0.07 (0.48), 122
Psychologist visits	0.00, 145	0.00, 130	0.07 (0.53), 118
Counsellor visits	0.02 (0.19), 144	0.02 (0.15), 127	0.07 (0.47), 118
Day hospital visits	0.29 (0.80), 146	0.62 (1.82), 131	0.44 (1.36), 119

TABLE 38 Costs (£) at each follow-up: drain insertion and talc slurry

	Time point, mean (SD), *n*		
Type of resource use	1 month	3 months	6 months
General practice consultations			
Surgery	14 (23), 133	22 (42), 121	27 (53), 125
Home	16 (66), 134	18 (72), 122	23 (75), 123
Telephone	6 (19), 134	11 (28), 119	6 (20), 121
Outpatient visits	173 (190), 146	280 (303), 140	283 (377), 142
A&E visits	17 (51), 147	28 (71), 143	26 (73), 142
Ambulance use	13 (51), 144	26 (78), 138	18 (78), 138
Hospitalisations	843 (2019), 148	1166 (2801), 143	1115 (2812), 143
Hospice care			
Inpatient stays	3 (34), 139	39 (259), 133	395 (2814), 130
Hospice nurse visits	20 (76), 138	28 (114), 127	20 (93), 125
Nurse consultations			
Clinic	12 (18), 140	13 (26), 130	13 (29), 127
Home	29 (95), 137	131 (362), 124	126 (319), 120
Physiotherapist visits	5 (26), 139	3 (19), 125	3 (20), 124
Occupational therapist visits	4 (22), 138	6 (38), 125	5 (23), 122
Psychologist visits	4 (25), 139	4 (40), 125	2 (27), 124
Counsellor visits	2 (18), 138	6 (68), 125	8 (55), 124
Day hospital visits	208 (728), 138	600 (1662), 130	667 (2041), 128

TABLE 39 Costs (£) at each follow-up: thoracoscopy and talc poudrage

Type of resource use	Time point, mean (SD), *n*		
	1 month	3 months	6 months
General practice consultations			
Surgery	12 (22), 142	25 (37), 116	19 (36), 110
Home	15 (45), 141	19 (56), 114	26 (76), 110
Telephone	5 (16), 141	10 (22), 115	12 (33), 109
Outpatient visits	151 (181), 152	253 (285), 144	280 (374), 134
A&E visits	21 (57), 152	26 (69), 144	23 (62), 133
Ambulance use	17 (66), 152	12 (49), 141	16 (67), 131
Hospitalisations	1100 (2495), 151	1674 (4272), 144	883 (2459), 137
Hospice care			
Inpatient stays	52 (418), 145	217 (1203), 132	309 (1649), 121
Hospice nurse visits	52 (418), 145	70 (605), 126	12 (73), 114
Nurse consultations			
Clinic	8 (13), 145	11 (19), 129	13 (29), 124
Home	38 (131), 143	121 (408), 120	110 (431), 113
Physiotherapist visits	2 (11), 146	4 (20), 127	9 (43), 121
Occupational therapist visits	5 (25), 145	6 (30), 127	5 (33), 122
Psychologist visits	0, 145	0, 130	10 (80), 118
Counsellor visits	3 (28), 144	4 (23), 127	10 (70), 118
Day hospital visits	212 (586), 146	455 (1340), 131	321 (1003), 119

TABLE 40 Complete and missing resource-use data at the 1-month follow-up

Type of resource use	Data, *n* (%)				
	Available			Missing	
	Alive	Dead within follow-up window	Dead before follow-up	Alive	Dead within follow-up window
***Thoracoscopy and poudrage* (N = *166*)**					
General practice consultations					
Surgery	134 (81)	8 (5)	N/A	22 (13)	2 (1)
Home	133 (80)	5 (3)	N/A	23 (14)	2 (1)
Telephone	133 (80)	8 (5)	N/A	23 (14)	2 (1)
Outpatient visits	144 (87)	8 (5)	N/A	12 (7)	2 (1)
A&E visits	144 (87)	8 (5)	N/A	12 (7)	2 (1)
Ambulance use	144 (87)	8 (5)	N/A	12 (7)	2 (1)
Hospitalisations	143 (86)	8 (5)	N/A	13 (8)	2 (1)

TABLE 40 Complete and missing resource-use data at the 1-month follow-up (*continued*)

Type of resource use	Data, *n* (%)				
	Available			Missing	
	Alive	Dead within follow-up window	Dead before follow-up	Alive	Dead within follow-up window
Hospice care					
Inpatient stays	138 (83)	7 (4)	N/A	18 (11)	3 (2)
Hospice nurse visits	136 (82)	8 (5)	N/A	20 (12)	2 (1)
Nurse consultations					
Clinic	137 (83)	8 (5)	N/A	19 (11)	2 (1)
Home	135 (81)	8 (5)	N/A	21 (13)	2 (1)
Physiotherapist visits	138 (83)	8 (5)	N/A	18 (11)	2 (1)
Occupational therapist visits	137 (83)	8 (5)	N/A	19 (11)	2 (1)
Psychologist visits	137 (83)	8 (5)	N/A	19 (11)	2 (1)
Counsellor visits	136 (82)	8 (5)	N/A	20 (12)	2 (1)
Day hospital visits	138 (83)	8 (5)	N/A	18 (11)	2 (1)
***Chest drain and slurry* (N = *164*)**					
General practice consultations					
Surgery	128 (78)	5 (3)	N/A	22 (13)	9 (5)
Home	129 (79)	5 (3)	N/A	21 (13)	9 (5)
Telephone	129 (79)	5 (3)	N/A	21 (13)	9 (5)
Outpatient visits	139 (85)	7 (4)	N/A	11 (7)	7 (4)
A&E visits	140 (85)	7 (4)	N/A	10 (7)	7 (4)
Ambulance use	137 (84)	7 (4)	N/A	13 (8)	7 (4)
Hospitalisations	141 (86)	7 (4)	N/A	9 (5)	7 (4)
Hospice care					
Inpatient stays	134 (82)	5 (3)	N/A	16 (10)	9 (5)
Hospice nurse visits	133 (81)	5 (3)	N/A	17 (10)	9 (5)
Nurse consultations					
Clinic	134 (82)	6 (4)	N/A	16 (10)	8 (5)
Home	131 (80)	6 (4)	N/A	19 (12)	8 (5)
Physiotherapist visits	133 (81)	6 (4)	N/A	17 (10)	8 (5)
Occupational therapist visits	132 (80)	6 (4)	N/A	18 (11)	8 (5)
Psychologist visits	133 (81)	6 (4)	N/A	17 (10)	8 (5)
Counsellor visits	132 (80)	6 (4)	N/A	18 (11)	8 (5)
Day hospital visits	132 (80)	6 (4)	N/A	18 (11)	8 (5)

N/A, not applicable.

TABLE 41 Complete and missing resource-use data at the 3-month follow-up

Type of resource use	Data, *n* (%)				
	Available			Missing	
	Alive	Dead within follow-up window	Dead before follow-up	Alive	Dead within follow-up window
***Thoracoscopy and poudrage* (N = *166*)**					
General practice consultations					
Surgery	98 (59)	8 (5)	10 (6)	33 (20)	17 (10)
Home	96 (58)	8 (5)	10 (6)	35 (21)	17 (10)
Telephone	98 (59)	7 (4)	10 (6)	33 (20)	18 (11)
Outpatient visits	114 (69)	20 (12)	10 (6)	17 (10)	5 (3)
A&E visits	115 (69)	19 (11)	10 (6)	16 (10)	6 (4)
Ambulance use	113 (68)	18 (11)	10 (6)	18 (11)	7 (4)
Hospitalisations	115 (69)	19 (11)	10 (6)	16 (10)	6 (4)
Hospice care					
Inpatient stays	110 (67)	12 (7)	10 (6)	21 (13)	13 (8)
Hospice nurse visits	105 (63)	11 (7)	10 (6)	26 (16)	14 (8)
Nurse consultations					
Clinic	105 (63)	14 (8)	10 (6)	26 (16)	11 (7)
Home	103 (62)	7 (4)	10 (6)	28 (17)	18 (11)
Physiotherapist visits	107 (65)	10 (6)	10 (6)	24 (14)	15 (9)
Occupational therapist visits	107 (65)	10 (6)	10 (6)	24 (14)	15 (9)
Psychologist visits	109 (66)	11 (7)	10 (6)	22 (13)	14 (8)
Counsellor visits	107 (65)	10 (6)	10 (6)	24 (14)	15 (9)
Day hospital visits	108 (65)	13 (8)	10 (6)	23 (14)	12 (8)
***Chest drain and slurry* (N = *164*)**					
General practice consultations					
Surgery	99 (60)	8 (5)	14 (9)	23 (14)	20 (12)
Home	99 (60)	9 (5)	14 (9)	23 (14)	19 (12)
Telephone	98 (60)	7 (4)	14 (9)	24 (15)	21 (13)
Outpatient visits	104 (63)	22 (14)	14 (9)	18 (11)	6 (4)
A&E visits	107 (66)	22 (14)	14 (9)	15 (9)	6 (4)
Ambulance use	106 (65)	18 (11)	14 (9)	16 (10)	10 (6)
Hospitalisations	107 (66)	22 (14)	14 (9)	15 (9)	6 (4)
Hospice care					
Inpatient stays	106 (65)	13 (8)	14 (9)	16 (10)	15 (9)
Hospice nurse visits	103 (63)	10 (6)	14 (9)	19 (12)	18 (11)
Nurse consultations					
Clinic	100 (61)	16 (10)	14 (9)	22 (13)	12 (7)
Home	100 (61)	10 (6)	14 (9)	22 (13)	18 (11)
Physiotherapist visits	100 (61)	11 (7)	14 (9)	22 (13)	17 (10)
Occupational therapist visits	100 (61)	11 (7)	14 (9)	22 (13)	17 (10)
Psychologist visits	100 (61)	11 (7)	14 (9)	22 (13)	17 (10)
Counsellor visits	100 (61)	11 (7)	14 (9)	22 (13)	17 (10)
Day hospital visits	102 (62)	14 (9)	14 (9)	20 (12)	14 (9)

TABLE 42 Complete and missing resource-use data at the 6-month follow-up

Type of resource use	Data, *n* (%)				
	Available			Missing	
	Alive	Dead within follow-up window	Dead before follow-up	Alive	Dead within follow-up window
***Thoracoscopy and poudrage* (N = *166*)**					
General practice consultations					
Surgery	70 (42)	5 (3)	35 (21)	32 (19)	24 (14)
Home	70 (42)	5 (3)	35 (21)	32 (19)	24 (14)
Telephone	69 (42)	5 (3)	35 (21)	33 (20)	24 (14)
Outpatient visits	79 (48)	20 (12)	35 (21)	23 (14)	9 (5)
A&E visits	78 (47)	20 (12)	35 (21)	24 (14)	9 (5)
Ambulance use	77 (46)	19 (11)	35 (21)	25 (15)	10 (6)
Hospitalisations	81 (49)	21 (13)	35 (21)	21 (13)	8 (5)
Hospice care					
Inpatient stays	75 (45)	11 (7)	35 (21)	27 (16)	18 (11)
Hospice nurse visits	72 (43)	7 (4)	35 (21)	30 (18)	22 (13)
Nurse consultations					
Clinic	76 (46)	13 (8)	35 (21)	26 (16)	16 (10)
Home	73 (44)	5 (3)	35 (21)	29 (17)	24 (14)
Physiotherapist visits	74 (45)	12 (7)	35 (21)	28 (17)	17 (10)
Occupational therapist visits	75 (45)	12 (7)	35 (21)	27 (16)	17 (10)
Psychologist visits	74 (45)	9 (5)	35 (21)	28 (17)	20 (12)
Counsellor visits	74 (45)	9 (5)	35 (21)	28 (17)	20 (12)
Day hospital visits	74 (45)	10 (6)	35 (21)	28 (17)	19 (11)
***Chest drain and slurry* (N = *164*)**					
General practice consultations					
Surgery	75 (46)	8 (5)	42 (26)	23 (14)	16 (10)
Home	75 (46)	6 (4)	42 (26)	23 (14)	18 (11)
Telephone	74 (45)	5 (3)	42 (26)	24 (15)	19 (12)
Outpatient visits	82 (50)	18 (11)	42 (26)	16 (10)	6 (4)
A&E visits	81 (49)	19 (12)	42 (26)	17 (10)	5 (3)
Ambulance use	81 (49)	15 (9)	42 (26)	17 (10)	9 (5)
Hospitalisations	82 (50)	19 (12)	42 (26)	16 (10)	5 (3)
Hospice care					
Inpatient stays	78 (48)	10 (6)	42 (26)	20 (12)	14 (9)
Hospice nurse visits	76 (46)	7 (4)	42 (26)	22 (13)	17 (10)
Nurse consultations					
Clinic	76 (46)	9 (5)	42 (26)	22 (13)	15 (9)
Home	74 (45)	4 (2)	42 (26)	24 (15)	20 (12)

continued

TABLE 42 Complete and missing resource-use data at the 6-month follow-up (*continued*)

Type of resource use	Data, *n* (%)				
	Available			Missing	
	Alive	Dead within follow-up window	Dead before follow-up	Alive	Dead within follow-up window
Physiotherapist visits	74 (54)	8 (5)	42 (26)	24 (15)	16 (10)
Occupational therapist visits	73 (45)	7 (4)	42 (26)	25 (15)	17 (10)
Psychologist visits	75 (46)	7 (4)	42 (26)	23 (14)	17 (10)
Counsellor visits	75 (46)	7 (4)	42 (26)	23 (14)	17 (10)
Day hospital visits	78 (48)	8 (5)	42 (26)	20 (12)	16 (10)

Appendix 3 The TAPPS trial 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 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 thoracoscopies 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 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. 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.

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