North Bristol NHS
NHS Trust

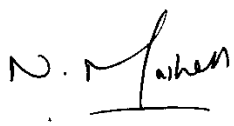
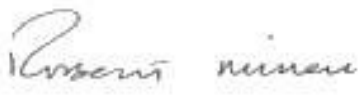
Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry

TAPPS trial

STATISTICAL ANALYSIS PLAN

Version 2.0
23rd April 2018

ISRCTN	**47845793**
REC	**12/NW/0467**
HTA Project Number	**10/50/42**

Authorised by	Signature	Date
Brennan Kahan **Trial statistician** B.Kahan@qmul.ac.uk		23rd April 2018
Nick Maskell **Chief Investigator** Nick.Maskell@bristol.ac.uk		23rd April 2018
Robert Miller **Trial Steering Committee Chair** Robert.Miller@ucl.ac.uk		23rd April 2018

1. BACKGROUND AND DESIGN

The main characteristics of this trial are summarised in the latest TAPPS trial protocol. Please refer to this for full details.

1.1 Trial summary

Malignant pleural effusions (MPE) are a major cause of morbidity amongst cancer patients, usually leading to significant breathlessness. Currently, there are about 250,000 new cases per year in the United States and the UK, which causes a heavy burden on healthcare services.[1] Median survival from diagnosis is typically only around 4-6 months.[2]

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

Thoracoscopy is becoming more widely available in the UK and is used frequently to perform talc poudrage. Our own audit data has suggested a benefit to using this approach over bedside talc slurry, although the published trials in this area have been few and have suffered from methodological flaws.[3] There are also potential benefits in patients' quality of life, and costs to healthcare providers in using poudrage, as this procedure usually involves a shorter hospital stay.

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

1.2 Patient eligibility criteria

1.2.1 Inclusion criteria

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

1.2.2 Exclusion criteria

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

1.3 Trial intervention

Patients will be randomised, in a 1:1 ratio using minimisation with a random element, to undergo either chest drain insertion with talc slurry pleurodesis or thoracoscopy with talc poudrage. Randomisation will be performed using a central telephone service and will take place following consent. The allocated trial intervention will take place within 72 hours of the allocation being determined.

Due to the inherent and substantial differences between the two methods being tested, this trial cannot be performed ethically or safely in a blinded manner using dummy or sham procedures. The trial will therefore be undertaken in an open-label manner, such that both the trial participant and the research team are aware of the allocated intervention.

1.4 Bias reduction

Due to the open-label nature of this trial, the potential for introducing bias into data collection and analysis is inherently greater than if the trial were performed in a fully blind fashion, especially given that it will typically be the local trial research teams who are 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 will be discussed with a blinded assessor.

1.5 Changes from v1.0 of the Statistical Analysis Plan

- Changed method of analysis for pleurodesis failure from competing risk time-to-event model to logistic regression model (as 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'. This was because:
    - Blinded assessment and corroboration of the need for pleural intervention were already required for any case which is likely to be contentious, as per section 1.4 above.
    - Without clinical contact, the information upon which the assessment would be made was felt to be insufficient to determine whether a further pleural procedure would have been necessary, and thus the clinical relevance of the outcome was felt to be doubtful
    - It is likely that this assessment would rely primarily on the patient's x-ray appearance, which is being addressed as another secondary outcome.
- Restricted subgroup analyses to only the primary outcome
- Updated Stata command for analysing chest x-ray pleural opacification, EQ-5D, SF36, 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 measure pleurodesis failure from date of procedure rather than date of randomisation.
- Removed the subgroup analysis for use of NSAIDs at baseline as this question has now been addressed in the TIME1 trial
- Removed the subgroup analysis for previous radiotherapy at baseline
- Added additional exploratory outcomes
- Specified that adverse events and serious adverse events would be summarised and analysed within 7 days of randomisation (in addition to within 30 and 180 days)

All changes to the Statistical Analysis Plan were made before database lock.

2. OUTCOME MEASURES

2.1 Primary outcome measure

2.1.1 Primary outcome measure description

The primary endpoint is the number of patients who experience pleurodesis failure up to three months (90 days) post randomisation. The overall survival rate from diagnosis of malignant pleural effusion is generally only a few months. For this reason, the primary endpoint being measured at three months is likely to be a more clinically relevant period over which pleurodesis failure will impact on patient care and quality of life. The proportion of patients experiencing pleurodesis failure by 1 and 6 months (30 days and 180 days) will be secondary outcomes.

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

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

A patient is also deemed to have failed pleurodesis if their primary physician decides that they require one of the above pleural interventions, but the intervention is not performed (e.g. in the event of death or patient choice against procedure). A patient who does not meet the criteria for a pleurodesis failure will be deemed as having had a successful pleurodesis.

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

2.2 Secondary outcome measures

2.2.1 Secondary outcome measures description

- 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 (chest x-ray) pleural opacification at the 1-month, 3-month and 6-month post randomisation follow-up visits, and after initial drain removal.
- Self-reported health-related quality of life at the 1-month, 3-month and 6-month follow-up post-randomisation visits, as measured using the SF-36 and EQ-5D questionnaires.
- Self-reported thoracic pain and breathlessness at 7, 30, 90 and 180 days post randomisation, measured using visual-analogue scale (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

2.2.2 Clarification of secondary endpoints

Percentage chest x-ray opacification

Percentage chest x-ray opacification will be assessed by two independent clinicians, at least one of whom is a radiologist. Both will be blind to treatment allocation. They will be asked to provide a measurement of percentage hemithorax opacification due to pleural effusion using an established

method.[4] Briefly, using appropriate radiological software, separate polygons are drawn by hand around both the hemithorax the pleural effusion. The size of the effusion is given as the ratio of the area of one polygon to the other. Both assessors will be asked to agree rescored values if there is a discrepancy of more than 15% between their two original measurements. The final value will be calculated from the mean of the two assessors' measurements.

Assessments of effusion size will only be made up to the point when a patient undergoes any intervention for fluid management on the side of the trial procedure.

2.3 Exploratory outcomes (added during the trial)

- Categorical version of percentage radiographic (chest x-ray) pleural opacification at the 1-month, 3-month and 6-month post randomisation follow-up visits, and after initial drain removal, with categories as:
    1. No fluid visible
    2. 1-24% opacification due to fluid (small effusion)
    3. 25-49% due opacification due to fluid (moderate effusion)
    4. 50% or greater opacification due to fluid (large effusion)

- Degree of visible lung entrapment on chest x-ray at 6 months post-randomisation. Categories are:
    1. No lung entrapment
    2. Minor lung entrapment (1-24% unexpanded lung)
    3. Moderate lung entrapment (25-49% unexpanded lung)
    4. Severe lung entrapment (50% or greater unexpanded lung)

Assessment of lung entrapment will be made by the same clinicians assessing pleural opacification.

3. SAMPLE SIZE

Previous literature and our own audit data suggest that patients with a WHO performance status score of 2 or better have approximate pleurodesis failure rates of 10% with a thoracoscopy, and 30% with standard chest tube and talc slurry pleurodesis.[5]

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

4. DATA CAPTURE AND MANAGEMENT

4.1 CRF descriptions and collection schedule

CRF	Frequency of collection	CRF description	Usual time of CRF completion
Enrolment	Once	Collection of baseline characteristics	Immediately after consent
Randomisation	Once	Inclusion/Exclusion criteria and minimisation information.	Immediately after enrolment
Chest drain insertion / Thoracoscopy and poudrage	Once. Only one form to be completed.	Collection of data relating to treatment arm procedure	Immediately after procedure performed
Discharge	Once	Collection of data relating to inpatient period and post-procedure complications	Around time of discharge
Follow-up	At each follow-up visit	Collection of data relating to pleurodesis failure and other follow-up information	Months 1, 3 and 6 post randomisation
Health service use questionnaire	At each follow-up visit	Collection of health economic data relating to post discharge period	Months 1, 3 and 6 post randomisation

4.2 Trial data management

4.2.1 Day to day data management

A trial database will be established by the Oxford Respiratory Trials Unit using the OpenClinica system. Data will be collected on the above CRFs and sent to the database manager, who will assume responsibility for data entry and data management until the database is locked. CRF data of all randomised patients will be entered onto the database using a single data entry process. All transcribed CRFs will be checked for inconsistent, ambiguous or missing information. The presence of any of these will lead to the generation of a data query. Data queries will be dealt with by the trial manager and database manager. The trial database will be amended on receipt of a response to a data query.

4.2.2 At time of analysis

On a date agreed by the Trial Steering Committee and the Trial statistician, the database manager will generate a trial dataset from the OpenClinica database. This will act as the frozen dataset. If further data queries are then raised by the trial statistician then the database may be changed based upon the responses to the queries. This will be done under the oversight of the trial statistician and the trial manager. After this, the database will be locked.

5. ANALYSIS PRINCIPLES

5.1 General principles for analysis

The primary analysis for each outcome will be by intention-to-treat, meaning that all patients on whom an outcome is available will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. More information on which patients are considered to have an available outcome is available in later sections. All tests will be two-sided, and will be considered statistically significant at the 5% level.

For each analysis, the following summaries will be provided:

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

All analyses will adjust for the minimisation variables (type of underlying malignant disease [mesothelioma, lung cancer, breast cancer, other] and WHO performance status [0-1 or 2-3]).[6-8] Minimisation variables will be included as covariates in the regression model for each outcome.

5.2 Interim analysis

No Interim analyses are planned for this study. However, primary outcome data will be reviewed regularly by the independent data monitoring committee (IDMC) alongside safety data. The IDMC may recommend early trial cessation to the trial steering committee (TSC) based upon such data.

5.3 Analysis of primary outcome

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

5.4 Analysis of secondary outcomes

5.4.1 Pleurodesis failure at 30 days post randomisation

Data will be analysed in the same manner as the primary outcome, using a logistic regression model.

5.4.2 Pleurodesis failure at 180 days post randomisation

Data will be analysed in the same manner as the primary outcome and as for pleurodesis failure at 30 days post randomisation.

5.4.3 Percentage radiographic (chest x-ray) pleural opacification

The percentage chest x-ray pleural opacification will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. Treatment effects will be presented for the discharge, 1-month, 3-month and 6-month follow-up visits.

The analysis will be performed in Stata as follows:

mixed *outcome treat##time covariates || subject id:,*
noconstant residual(unstructured, t(time))

where *outcome* refers to the chest x-ray pleural opacification value, *treat* refers to the treatment variable, *time* refers to the study visit, and *covariates* refers to the covariates to be included in the analysis, which are the minimisation factors.

5.4.4 EQ-5D

Self-reported quality of life using the EQ-5D questionnaire will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. In addition to the minimisation factors, the analysis will also adjust for baseline EQ-5D. Missing values of baseline EQ-5D will be imputed using mean imputation [9]. Treatment effects will be presented for the 1-month, 3-month and 6-month follow-up visits. The Stata code used for analysis is the same as for pleural opacification above.

5.4.5 SF-36

The SF-36 health questionnaire will be analysed in the same manner as the EQ-5D.

5.4.6 Thoracic pain

Self-reported VAS scores for thoracic pain will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. The analysis will adjust for the baseline value of thoracic pain (in addition to the minimisation factors, as mentioned in section 5.1). Missing baseline values of thoracic pain will be imputed using mean imputation. Treatment effects will be presented for the 1-month, 3-month and 6-month follow-up visits, and for the 7 days post randomisation. The Stata code used for analysis is the same as for pleural opacification above.

5.4.7 Breathlessness

Self-reported VAS scores for breathlessness will be analysed using the same methods as for thoracic pain.

5.4.8 Mortality

All-cause mortality up to 180 days post randomisation will be analysed using a logistic regression model.

5.4.9 Time to pleurodesis failure from randomisation

Time to pleurodesis failure will be analysed using a competing risk time-to-event regression model, with mortality as the competing risk. Patients who do not experience either the primary outcome or mortality will be censored at the point of last contact.

5.4.10 Number of days spent as a hospital inpatient up to 90 days post randomisation

The number of days spent as an inpatient from randomisation up to 90 days post randomisation will be analysed using a negative binomial regression model. The number of days of follow-up will be included in the model as an offset (i.e. the model will include a term for the log-transformed number of days of follow-up for each patient, with the parameter constrained to one).

5.4.11 Adverse events

Adverse events will be analysed using a logistic regression model. Analyses will be performed for adverse events up to 7, 30, and 180 days post-randomisation.

5.4.12 Serious adverse events

Serious adverse events will be analysed using a logistic regression model. Analyses will be performed for serious adverse events up to 7, 30, and 180 days post-randomisation.

5.4.13 Exploratory outcomes

The exploratory outcome of the categorical version of percentage radiographic pleural opacification will be analysed using a mixed-effects ordinal logistic regression model, with a random-intercept for patient. The model will be adjusted for the minimisation variables.

The exploratory outcome of the degree of visible lung entrapment will be analysed using an ordinal logistic regression model, adjusted for the minimisation variables.

5.5 Subgroup analyses

Subgroup analyses will be performed for the primary outcome. An interaction test will be used (i.e. an interaction term between the treatment and the baseline covariate will be added to the regression model), and will be considered statistically significant at the 5% level. Results from subgroup analyses will be viewed as hypothesis generating, and will not be used to make definitive statements about treatment efficacy in a specific subgroup of patients. The following subgroup analyses will be performed:

- Patients receiving anti-cancer therapy at baseline vs those not receiving anti-cancer therapy at baseline
- WHO performance status 0 vs 1 vs 2 vs 3
- Patients on steroids at baseline vs those not on steroids at baseline
- Previous attempt at pleurodesis within the last month vs. no attempt in the last month.
- Patients with primary malignancy of breast cancer vs. mesothelioma vs. lung cancer vs. other

5.6 Missing data

5.6.1 General comments

The primary outcome will be considered missing if there is no data regarding pleurodesis failure during the first 90 days post-randomisation. Secondary outcomes measuring pleurodesis failure will also be regarded as missing if there is no data available up to the specific time point.

EQ-5D, SF-36, and VAS for thoracic pain and breathlessness will be considered missing if no post-randomisation measurements are recorded.

Number of days in hospital, adverse events, and serious adverse events will be considered missing if the patient attends no follow-up visits, and outcome records are not available.

Chest x-ray opacification will be considered missing if there are no available x-ray data for analysis.

All-cause mortality will be considered missing if we are unable to obtain information on whether the patient was alive at the end of follow-up.

5.6.2 Deviations from prescribed follow-up windows

In order to ensure representative data for each data collection time-point, any time-point-specific trial data (quality of life and symptom scores) generated outside of the following windows will be regarded as missing and will not be used towards analysis:

- "One month visit" – Day 21 post randomisation to day 56 post randomisation
- "Three month visit" – Day 70 to day 112
- "Six month visit" – Day 140 to day 196

5.7 Sensitivity analyses

5.7.1 Missing data

Sensitivity to missing data for the primary outcome will be assessed under a range of missing-not-at-random scenarios. This will be performed using the following formula:

$$\Delta = \Delta_{CC} + Y_1P_1 - Y_2P_2$$

where Δ is the treatment effect under the missing-not-at-random scenario, Δ_{CC} is the treatment effect under a complete case scenario (i.e. where patients with a missing outcome are excluded), P_1 and P_2 are the proportion of patients who were excluded in groups 1 and 2 respectively, and Y_1 and Y_2 are the proportion of patients in treatment group 1 and 2 with missing data who are assumed to experience an event (i.e. who experience the primary outcome). For this sensitivity analysis, we will consider all patients who were excluded from the primary analysis due to missing data. We assume that the standard error for Δ is approximately equal to the standard error for $\Delta_{CC.}$

Y_2 will be varied between 10%, 25%, 50%, 75%, and 90% and for each value of Y_2, Y_1 will be varied between Y_2-10%, Y_2, and Y_2+10%. For example, for Y_2=25%, Y_1 will vary between 15%, 25%, and 35%.

For each scenario, a treatment effect and 95% confidence interval will be calculated, which will be compared with results from the main analysis of the primary outcome to see if conclusions are affected by different assumptions regarding the missing data.

5.8 Further studies

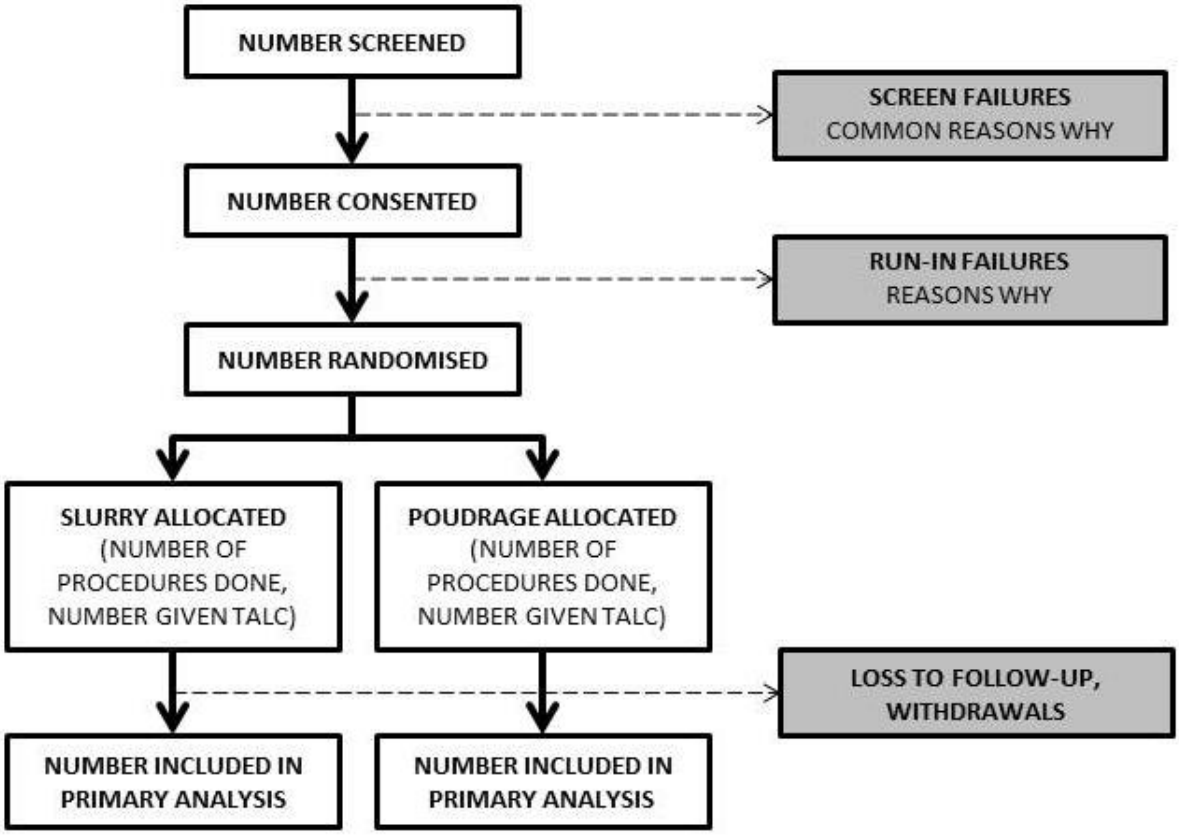
In addition to the above, data being collected as part of the TAPPS trial may also be used to undertake further sub-studies, the details of which are beyond the scope of this analysis plan. These may include, but are not limited to:

- A full health economic analysis
- Analysis of genetic markers associated with pleurodesis success or failure

6. DATA SUMMARIES

6.1 CONSORT flow chart

The following information will be provided in the form of a flow chart:



6.2 Summary graphs

The following outcomes will be displayed in the form of Kaplan-Meier survival curves:

- Pleurodesis failure up to 180 days post randomisation (primary outcome)
- All-cause mortality

The following outcomes will be displayed in the form of two adjacent graphs; the first detailing the raw scores for the outcome (beginning with the baseline value) according to each treatment arm, and the second demonstrating the treatment effect. Each graph will indicate 95% confidence intervals (the first graph for the mean outcome at that time point, and the second graph for the treatment effect) and will provide measurements at the 1-month, 3-month and 6-month time points:

- Percentage chest x-ray opacification
- Quality of life measures (EQ-5D and SF-36)
- VAS scores (for breathlessness and thoracic pain)

6.3 Further data summaries

- Incidence of lung entrapment on 18-24 hour CXR

- Incidence of lung entrapment on discharge or drain removal CXR

6.4 Tables

6.4.1 Table 1 - Baseline characteristics

	Talc slurry (n=…)	Talc poudrage (n=…)	Number missing (slurry, poudrage)
Age – mean (SD)			
Male – no. (%)			
Smoking status – no. (%)			
Current smoker			
Ex-smoker			
Never-smoker			
WHO performance status at randomisation – no. (%)			
0			
1			
2			
3			
Underlying cancer type – no. (%)			
Lung			
Mesothelioma			
Breast			
Ovarian			
Lymphoma			
Upper GI			
Lower GI			
Renal			
Unknown primary			
Other			
Side of effusion needing intervention			
Left			
Right			
Size of effusion at baseline (percentage opacification)			
Size of effusion at baseline (by category)			
0 (none)			
1 (small)			
2 (moderate)			
3 (large)			
Previous pleural intervention on same side of effusion in previous 3 months – no. (%)			
Attempt at pleurodesis on intervention side in last month – no. (%)			
Attempt at pleurodesis on the intervention side at any time in the past – no. (%)			

Duration of symptoms from effusion – no. (%)			
Less than one week			
1 to 3 weeks			
More than 3 weeks			
Chest pain (VAS) at randomisation – mean (SD)			
Breathlessness (VAS) at randomisation – mean (SD)			
NSAIDs at baseline – no. (%)			
Oral steroids at baseline – no. (%)			
Analgesia at baseline – no. (%)			
Simple/weak opiate only			
Strong opiate			
Previous radiotherapy to chest – no. (%)			
Any form of cancer treatment at baseline - no. (%)			
Significant respiratory disease – no. (%)			
Significant cardiac disease – no. (%)			

6.4.2 Table 2 – Results relating to trial interventions and inpatient stay

	Talc slurry (n=…)	Talc poudrage (n=…)	Number missing (slurry, poudrage)
Duration of procedure			
Grade of operator			
Total fluid drained as inpatient			
Complications during procedure			
Complications in 2 hours post talc			
Drain size used (median)			
Thoracic suction used			
Time drain in situ			
Time from randomisation to allocated procedure-mean (SD)			
Time from allocated procedure to discharge-mean(SD)			

6.4.3 Table 3 - Results for pleurodesis failure

	Number included in analysis		Summary measure			
Outcome	Slurry (n=…)	Poudrage (n=…)	Slurry	Poudrage	Treatment effect (Slurry vs. Poudrage) and 95% CI	P-value
Number experiencing pleurodesis failure at 30 days post randomisation – no. (%)						
Number experiencing pleurodesis failure at 90 days post randomisation – no. (%)						
Number experiencing pleurodesis failure at 180 days post randomisation – no. (%)						
Time to pleurodesis failure from randomisation						

6.4.4 Table 4 – Results for secondary outcomes

	Number included in analysis		Summary measure			
Outcome	Slurry (n=…)	Poudrage(n=…)	Slurry	Poudrage	Treatment effect (slurry vs. poudrage) and 95% CI	P-value
All-cause mortality up to 180 days post randomisation						
Hospital inpatient nights up to 90 days						
Thoracic pain – mean (SD)						
7 days						
1 month						
3 months						
6 months						
Breathlessness – mean (SD)						
7 days						
1 month						
3 months						
6 months						
EQ-5D – mean (SD)						

1 month						
3 months						
6 months						
SF-36 – mean (SD)						
1 month						
3 months						
6 months						
Chest x-ray opacification – mean (SD)						
1 month						
3 months						
6 months						
Adverse events – no. (%)						
Serious adverse events – no. (%)						

7. REFERENCES

1. Marel, M., et al., *The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia.* Chest, 1993. **104**(5): p. 1486-9.
2. Heffner, J.E., P.J. Nietert, and C. Barbieri, *Pleural fluid pH as a predictor of survival for patients with malignant pleural effusions.* Chest, 2000. **117**(1): p. 79-86.
3. Dresler, C.M., et al., *Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion.* Chest, 2005. **127**(3): p. 909-15.
4. Rahman, N.M., et al., *Intrapleural use of tissue plasminogen activator and DNase in pleural infection.* N Engl J Med, 2011. **365**(6): p. 518-26.
5. Rahman, N.M., et al., *Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010.* Thorax, 2010. **65 Suppl 2**: p. ii54-60.
6. Davies, H.E., et al., *Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial.* JAMA, 2012. **307**(22): p. 2383-9.
7. Kahan, B.C. and T.P. Morris, *Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis.* BMJ, 2012. **345**: p. e5840.
8. Kahan, B.C. and T.P. Morris, *Assessing potential sources of clustering in individually randomised trials.* BMC Med Res Methodol, 2013. **13**(1): p. 58.
9. White, I.R. and S.G. Thompson, *Adjusting for partially missing baseline measurements in randomized trials.* Stat Med, 2005. **24**(7): p. 993-1007.

8. ABBREVIATIONS

CI	Confidence interval
CRF	Case report form
CT	Computed tomography
CXR	Chest x-ray
IDMC	Independent data monitoring committee
IPC	Indwelling pleural catheter
IQR	Interquartile range
MPE	Malignant pleural effusion
MRI	Magnetic resonance imaging
No.	Number
NSAID	Non-steroidal anti-inflammatory drug
SD	Standard deviation
TSC	Trial steering committee
UK	United Kingdom
VAS	Visual analogue scale
WHO	World health organisation