Title: Role of thoracic ultrasound in pleurodesis pathways for malignant pleural effusions: the SIMPLE randomised trial

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Summary

Background

Pleurodesis is performed as an in-patient procedure to control symptomatic recurrent malignant pleural effusion (MPE) and has a success rate of 75-80%. Thoracic ultrasound (TUS) has been shown in a small study to predict pleurodesis success early by demonstrating cessation of lung sliding. This international trial investigated whether the use of TUS in pleurodesis pathways could shorten length of hospital stay (LOS) in MPE patients undergoing pleurodesis.

Methods

Patients were randomised to TUS-guided care or standard care in a 1:1 ratio. In the intervention group, daily TUS examination for lung sliding in nine regions was conducted to derive an 'adherence score' (min: 9, preserved sliding; max: 27, complete absence of sliding), and the chest tube was removed if the score was >20. In the standard care group, tube removal was based on daily output volume (per British Thoracic Society Guidelines). The primary outcome was LOS and secondary outcomes included pleurodesis failure at 3 months, time to tube removal, symptoms and quality-of-life scores and cost-effectiveness of TUS-guided care.

Findings

313 patients (52.7% males) were recruited; 159 randomised to TUS-guided care and 154 to standard care. The most common primaries were mesothelioma, lung and breast cancer. In the intention-to-treat population, the median [IQR] LOS was significantly shorter in the TUS group (2 [2-4] days) compared to standard care (3 [2-5] days, difference 1 day, p<0.001). In the per-protocol analysis TUS-guided care was non-inferior to standard care in terms of pleurodesis failure at 3 months which occurred in 29.7% of patients (27/91) in the TUS group vs 31.2% of patients (34/109) in the standard care group (risk difference -1.5%; 95% CI -10.2% to 7.2%, non-inferiority margin 15%). Mean (SD) time to chest tube removal in the TUS group was 2.4 (2.5) days vs. 3.1 (2.0) days in the standard group

(mean difference -0.72 (95% CI: -1.22 to -0.21) days, p=0.006). There were no significant between-group differences in the symptom or quality-of-life scores. Although costs were non-significantly smaller for TUS-guided care, it was cost-effective in comparison to standard care.

Interpretation

TUS-guided care for pleurodesis in patients with MPE results in shorter hospital stay (in comparison to the British Thoracic Society recommendation for pleurodesis) without reducing the success rate of the procedure at three months. The data support consideration of standard use of TUS in patients undergoing MPE-related pleurodesis.

Trial registration number: ISRCTN16441661

Research in context

Evidence before this study

The current British Thoracic Society (BTS) Pleural Disease Guidelines recommend for pleurodesis practice in malignant pleural effusion to monitor fluid output from chest tubes before and after performance of pleurodesis to decide on suitability of instituting the pleurodesing agent and chest tube removal. A search on PubMed for studies on pleurodesis practice in malignant pleural effusion published up to 24th March 2021 with key words "pleurodesis or sclerotherapy", "malignant pleural effusion", "ultrasound" and "drainage" was performed. This showed three case series and three randomised controlled trials studying the effect of relying on imaging confirmation (via radiograph or ultrasound) of lung re-expansion and/or removal of the chest tube 1-24 hours post pleurodesis. The results suggest that "alternative approaches" to pleurodesis are not less efficacious, but the risk of bias, particularly for observational studies was high. In addition, the randomised trials were either small or with methodological problems.

The current trial studied the impact of relying on ultrasound confirmation of lung re-expansion to decide on the time of pleurodesis and introduced a novel method of ultrasound examination of lung sliding as an evidence of pleurodesis (by observing loss of sliding) to decide on when a chest tube is ready to be removed.

Added value of this study

To our knowledge, this is the first adequately powered study demonstrating that the use of ultrasound to guide pleurodesis practice is at least as effective as the current approach recommended by the BTS, with the added benefit of reducing median length of hospital stay from three days with the standard method to two days with the ultrasound-guided approach.

Implications of all the available evidence

This highly novel study, as the first ever randomised trial in which treatment is directed by bedside ultrasound, challenges current treatment paradigms for patients with malignant pleural effusion who undergo talc pleurodesis. The study intervention is a simple procedure that relies on technology widely available in hospitals across the world.

Introduction

Malignant pleural effusion (MPE) develops in 15% of patients with cancer[1,2] and is the cause of 0.35% of all hospital admissions[3]. Patients with MPE have significant symptoms and up to 80% require therapeutic thoracentesis[4], but MPE recurs after drainage, and in two thirds of cases recurrence is within two weeks of initial drainage[5]. International guidelines recommend definitive intervention for recurrent MPE rather than repeat thoracentesis[2,6,7], with the options of pleurodesis and indwelling pleural catheter (IPC) insertion.

The choice between pleurodesis and IPC insertion is dependent on clinical factors (i.e. the presence of expandable lung following fluid drainage) and patient/clinician preference. Pleurodesis requires an initial hospital admission but has an overall success rate of effusion control of 75-80%[8]. IPC insertion can occur as a day-case procedure, but requires regular home drainage, and is associated with lower pleurodesis success rates of 50% even with daily drainage or intrapleural talc administration via the IPC[9–11]. Both procedures produce clinically meaningful improvement in dyspnea[12], but patients with IPC spend less time in hospital[13] at the expense of higher overall complications[2,7]. In recent years, there has been a trend towards increased use of IPC in MPE management in the USA[14]. However, talc pleurodesis remains a key treatment option, and recent data demonstrate that pleurodesis is the management of choice in 72% of patients with MPE undergoing definitive intervention[5]. Thus, optimising pleurodesis remains an important and clinically relevant area of investigation. Reducing time in hospital would significantly improve pleurodesis as a treatment option.

The current British Thoracic Society (BTS) Pleural Guidelines recommend that following talc pleurodesis, the chest tube should be removed when fluid volume drainage per 24 hours is below 250ml, and lung re-expansion is confirmed radiologically[6]. However, this recommendation is not based on strong evidence. Studies have shown that confirmation of adherence of pleural membranes in patients with pneumothorax who underwent surgical pleurodesis can be done using thoracic ultrasound (TUS) by demonstrating absence of 'lung sliding', a normal phenomenon seen in healthy

subjects[15]. The absence of lung sliding on TUS within 24 hours of talc slurry pleurodesis in patients with MPE was a predictor of pleurodesis success at one month[16]. Similarly, in patients with MPE who presented for IPC removal due to cessation of drainage, the presence of lung sliding was a predictor of fluid re-accumulation and need for further procedures within three months[17].

This randomised controlled trial aimed to investigate whether the use of TUS before and after pleurodesis, in comparison to current BTS guideline management, could shorten length of hospital stay (primary outcome) without reducing overall pleurodesis success at three months, and the time to chest tube removal, use of healthcare resources, cost-effectiveness of the procedure, symptoms and quality of life in the study groups (secondary outcomes).

Methods

Study Design and Setting

The Efficacy of Sonographic and Biological Pleurodesis Indicators of Malignant Pleural Effusion (SIMPLE) trial was an open-label randomised controlled trial of TUS-guided care versus standard care in patients admitted to hospital for talc pleurodesis to manage recurrent symptomatic MPE[18]. Eligible and consenting participants were assigned in a 1:1 ratio to receive either TUS-guided care (intervention group) or standard care (control group – see below). SIMPLE was an open-label trial as masking the intervention from participants or study staff was not practical.

The trial protocol was approved by the South Central-Oxford C Research Ethics Committee (Reference number 15/SC/0600) and was registered online (ID ISRCTN16441661). SIMPLE recruited in 10 UK centres and one centre in the Netherlands. The trial was funded by the Marie Curie Cancer Care Committee, Project Award C49481/A17178.

Participants

Consecutive participants aged $\geq$ 18 years diagnosed with MPE who required talc pleurodesis for symptom relief were invited to participate. Participants were eligible if they had a diagnosis of MPE which was confirmed either histo-cytologically, on computed tomography scanning, by macroscopic evidence of malignancy at thoracoscopy, or in the setting of unexplained exudative pleural effusion with an established diagnosis of cancer elsewhere. Participants receiving talc slurry via a chest tube or as poudrage during medical thoracoscopy were included. The decision to use talc slurry or poudrage was made by the treating physician and depended on the clinical indication. Exclusion criteria were 1) Contraindication to chest tube placement and 2) Poor prognosis (expected survival less than one month as judged by treating physician).

Randomisation

Randomisation was carried out via an online platform (Sealedenvelope.com; Clerkenwell Workshops, London, UK). A minimisation algorithm was used to ensure balance of participants across the two treatment groups, minimised by: 1) Recruiting centre, 2) Method of talc delivery intended (slurry vs. poudrage) and 3) LENT score. The LENT (pleural fluid LDH, Eastern Cooperative Oncology Group performance status score, blood Neutrophil to lymphocyte ratio and Tumour type) score is a three-tier prognostic score that predicts survival in patients with MPE[19]. The algorithm was designed to have a probabilistic element of 0.85 to ensure unpredictability of treatment assignment. An issue with the randomisation system meant the first 300 randomisations were not minimised on LENT score categories, a full description is provided in the supplementary material.

Trial procedures

Standard Care

The management of participants randomised to the standard care group followed the BTS guidelines[6]. Briefly, in participants planned to receive talc slurry, a small-bore chest tube ($\leq$ 18F) was inserted to allow complete drainage of effusion. Once drainage and re-expansion of the lung was confirmed on chest radiography, and daily output of the chest tube fell below 150 ml, talc slurry (4g) was administered via the chest tube. The tube was removed after at least 24 hours <u>and</u> when the tube output was < 250 ml per 24-hour period. In participants undergoing talc poudrage during thoracoscopy, all fluid was drained during the endoscopic procedure and a large-bore tube (>20F) inserted after talc powder (4g) was sprayed into the pleural cavity. The tube was removed after at least 24 hours <u>and</u> when lung re-expansion was confirmed radiologically <u>and</u> tube output was < 250 ml per day.

Intervention

In the TUS-guided care group, all TUS examinations were carried out using point of care ultrasound machines. The criterion for talc slurry instillation following chest tube insertion was confirmation of drainage of the effusion on TUS examination. Twenty-four hours following talc slurry application, a

TUS assessment of lung sliding at nine regions of the hemithorax of interest was carried out to reach an overall adherence score. These were 'upper', 'middle' and 'lower' regions at each of the three anatomical lines; mid-clavicular, mid-axillary and para-vertebral lines[18]. For each region, the TUS operator scored lung sliding based on dynamic TUS examination as: present (=1 point), questionable (=2 points) or absent (=3 points, total lowest possible score 9, highest possible score 27).

The chest tube was removed if the sum of scores was more than 20 or if the score was 3 for each of the three zones at the mid-axillary line[18]. TUS adherence scoring was repeated at 48 and 72 hours post talc administration if the adherence score was less than 21. In cases where the adherence score was below 21 at 72 hours post talc pleurodesis, management reverted to BTS guidelines (identical criteria to standard care). In participants undergoing talc poudrage, TUS adherence score was obtained 24 hours post poudrage and the criteria to remove the tube using the TUS score was identical to that in talc slurry pleurodesis.

The presence of trapped lung after pleural fluid drainage was defined as the absence of pleural apposition in more than two thirds of the hemithorax on post-drainage radiograph. In such situations the decision to perform pleurodesis was left to the discretion of the local investigator. Participants with trapped lung were not excluded from the trial but those randomised to TUS-guided care were managed per BTS criteria since TUS examination would not be feasible.

In all participants, a baseline and daily 100-mm visual analogue scale (VAS) score for chest pain and breathlessness was obtained. All participants were asked to complete a baseline EuroQoL Group 5-Dimension 5-Level (EQ-5D-5L) Questionnaire and 100-mm VAS.

Follow up

Two follow up trial assessments were carried out at 1-month and 3-months post randomisation. At each visit participants were asked to complete a VAS score for chest pain and breathlessness and the

EQ-5D-5L questionnaire and 100-mm VAS. Information on further ipsilateral pleural interventions was collected. A healthcare utilisation log was completed during both visits by all participants.

At 12 months post randomisation, mortality status was ascertained by accessing participant's medical records. Mortality data were available for the first 270 randomised participants; this visit was not included in the trial assessments of the additional participants who were recruited after reaching the initial sample size (see below).

Outcomes

Primary outcome

The primary outcome measure was length of hospital stay in days from randomisation until a participant was declared fit for discharge, on the basis of standard criteria in both treatment groups. In all study participants a chest radiograph was conducted shortly after chest tube removal and was reviewed by the clinical team. If the radiograph was deemed acceptable and the participant did not have other outstanding medical issues that require hospitalisation, they were declared medically fit for discharge.

Secondary outcomes

Pleurodesis success: the trial was powered to test non-inferiority of TUS-guided care compared to standard care for pleurodesis failure at three months, with a pre-defined non-inferiority margin of 15% change in failure rate (pre-hoc agreed by a panel of experts in previous studies[8]). Pleurodesis failure was defined as the need for further pleural intervention in the ipsilateral hemithorax.

Other key secondary outcomes included time (in days) to chest tube removal from randomisation, all-cause mortality, quality-of-life scores (EQ-5D-5L questionnaire), patient-reported symptom scores (chest pain and dyspnoea VAS), healthcare resource use and costs and cost-effectiveness. A further secondary outcome was assessment of biological (pleural fluid parameter) predictors of pleurodesis success – this study is reported elsewhere[20].

Sample size

Based on internal audit data at the time of study planning, and demonstrated in later clinical studies[21], mean hospital stay was 6 days (SD 4.5) for talc pleurodesis with standard care. Based on pilot data, we assumed that TUS would reduce hospital stay by 2 days. In order to demonstrate this difference at 90% power, a 5% two-sided significance level, and allowing for 5% attrition due to death before discharge, 254 participants were required. For the non-inferiority comparison of pleurodesis success, assuming mean pleurodesis success at 3 months to be 75% (as shown by previous clinical trials[8,12,13]), and a non-inferiority margin (delta) of 15% (agreed as clinically significant in other studies[8]), 262 participants were required to demonstrate non-inferiority (80% power, 2.5% one sided significance). As specified in the protocol, the Data and Safety Monitoring Committee assessed the overall hospital stay data at 50% recruitment (without direct comparison) in a closed session to check the assumptions of the sample size calculation. They reported that hospital stay was non-normally distributed with a SD of 6.3 days but with a lower attrition rate (4.5%) than had been assumed. This resulted in reduced power of the study at the previous target of 262 participants to 60% for the hospital stay outcome. This was discussed at the Trial Steering Committee and, based on power modelling conducted by the trial statisticians, the decision made was to increase recruitment to 344 participants to achieve 80% power.

Statistical analysis

Statistical methods for analysing trial data were specified in the protocol[18], and the statistical analysis plan is included in the supplement. Main analyses were performed for the intention-to-treat (ITT) population which included all participants analysed according to the group to which they were randomised. The per-protocol (PP) population excluded participants: (i) without a pleurodesis date; (ii) who were randomised and later found to be ineligible; (iii) who did not provide primary outcome

data; or (iv) participants in the TUS group with no recorded TUS data. A significance level of 0.05 was used throughout, and 95% confidence intervals were reported. The baseline comparability of the two intervention groups in terms of minimisation factors, baseline characteristics, and baseline values of patient-reported outcome measures was assessed for the ITT population.

Analysis of the primary outcome (initial length of hospital stay) was performed using a Mann-Whitney U-test due to departures from normality. This was performed for the ITT population using complete cases and sensitivity analyses included a best-case-worst-case analysis to explore the impact of data missing due to death and analysis of the PP population. An analysis adjusted for LENT score, talc delivery method and primary cancer diagnosis (lung vs mesothelioma vs others) as fixed effects and recruiting centre as a random effect was also conducted using a mixed effects linear regression model on the log transformed data, and Kaplan-Meier curves were used to summarise time to discharge.

The non-inferiority analysis of pleurodesis failure used an adjusted mixed effects logistic regression model and was performed for the PP population and repeated for the ITT population as a sensitivity analysis. Kaplan-Meier curves were used to summarise time to failure.

All other secondary outcomes were analysed for the ITT population using available cases. Time to chest tube removal was compared between groups using t-tests and adjusted mixed effects models. All-cause mortality was summarised using Kaplan-Meier curves and compared using a Cox proportional hazards model. EQ-5D-5L responses were converted into utility values using population valuations[22]. EQ5D utility and VAS scores and chest pain and dyspnoea VAS scores were compared using adjusted mixed effects linear regression models. For EQ5D utility scores, the suitability of the assumption of a score of 0 for those who had died was explored in a sensitivity analysis. Analyses were undertaken on Stata version 15.1 (StataCorp, College Station, TX).

Cost-effectiveness analysis

A within trial cost-effectiveness analysis, a plan of which is reported in the supplement, was done comparing the additional cost per Quality Adjusted Life-Year (QALY) gained when TUS-guided care was compared to standard care. The price year was 2019, and all costs were expressed in GB pounds.

Role of funding source

Results

Three-hundred and thirteen participants were recruited between 31st December 2015 and 17th December 2019. The trial was stopped prior to reaching the revised recruitment target of 344 participants due to slower than anticipated recruitment. The flow of participants through the trial is summarised in Figure 1 and reasons for exclusion summarised in Table S1. Baseline characteristics are summarised by treatment group in Tables 1 & S2. The groups were well-matched in the proportions of participants with different primary cancers, LENT score, pleurodesis method (i.e. size of chest tube and talc delivery method), and quality-of-life and symptom scores.

Data quality

The CONSORT flowchart detailing numbers of participants assessed for eligibility, excluded and randomised to each treatment group is shown in Figure 1. The number of participants providing follow-up data at each time point and contributing to the analysis of the primary and key secondary outcomes are summarised in Figure 1 and Table S3. Details of compliance are summarised by treatment group in Tables S4-6.

The ITT population consisted of all randomised participants (159 participants (50.8%) randomised to TUS-guided care and 154 participants (49.2%) randomised to standard care). The PP population consisted of 129 participants (48.1%) randomised to TUS-guided care and 139 participants (51.9%) randomised to standard care.

Details of withdrawals, loss to follow-up and protocol deviations are summarised in tables S5-6.

Primary outcome

The median length of stay in the TUS group (median = 2 days, IQR 2 to 4) was significantly shorter than in the standard care group (median = 3 days, IQR 2 to 5) with a difference of 1 day (95% CI 1 to 1 day, p<0.001). Length of stay is summarised by treatment group (Figure 2). None of the sensitivity analyses conducted changed the primary analysis results (Tables 2 & S7, see online supplement for details). Due to non-normality of the data, the adjusted analysis was performed on log transformed data and results are reported on the log scale (Table 2); when back-transformed this equates to a difference of

0.73 days (95% CI 0.63 to 0.84 days). As a post-hoc analysis, treatment effects are presented separately by site and for the two methods of talc administration and the size of chest tube (Figures S2 and S3A & B), the average length of stay in the TUS-guided care group is shorter than in the standard care group regardless of the method of talc administration or the chest tube size. Length of hospital stay data are also presented using a Kaplan-Meier plot (Figure S1).

<u>Secondary Outcomes</u>

Pleurodesis success

In the PP population the number of failures was similar in both groups, 27/91 (29.4%) in the TUS-guided care group compared to 34/109 (31.2%) in the standard care group. The confidence interval for the risk difference between the two groups did not cross the pre-specified non-inferiority margin (15%) thus demonstrating that TUS was non-inferior to standard care in terms of pleurodesis failure (Table 2, Figure 3). This was repeated for the ITT population which did not show a different result (Table 2, Figure 3). Kaplan-Meier survival curves are presented in Figure S4.

Time to chest tube removal

The average time to tube removal was significantly shorter in the TUS-guided care group (mean 2.4, SD 2.5 days) than in the standard care group (mean 3.1, SD 2.0 days) with a difference of 0.72 days (95% CI -1.22 to -0.21, p=0.006) between the groups. Sensitivity analysis using mixed effects models did not alter the result (Table 2). Kaplan-Meier time to tube removal is shown in Figure S6.

All-cause mortality and Safety

Mortality at 12-months (365 days) was not significantly different between treatment groups (HR = 1.10, 95% CI 0.79 to 1.55; see Table S8). Kaplan-Meier survival curves are presented in Figure S7. The number and proportion of participants for whom a talc-related adverse event was recorded on the discharge CRF is summarised by treatment group in Table S9.

Quality of life

EQ-5D utility scores and EQ-5D VAS from baseline to 3-months post randomisation were summarised by treatment group with adjusted differences between groups (Table 2 and Figures S8-9). There was no significant difference between groups at 1- or 3-months post-randomisation in the EQ-5D utility scores in the primary and sensitivity analyses. There was a significant difference in the EQ-5D VAS in favour of the TUS-guided care group at 3-months post-randomisation. Survival data were combined with EQ-5D-5L utilities to estimate QALYs at 3 months after randomisation. Patients randomised to TUS-guided care gained, over 3 months, an average of 0.128 (95% CI: 0.120 to 0.139) QALYs compared to 0.129 (95% CI: 0.118 to 0.139) in those randomised to standard care (mean difference: -0.001; 95% CI difference: -0.015 to 0.014).

Patient-reported chest pain and dyspnoea

Trends over time in VAS scores for chest pain and dyspnoea from baseline to the 1-month timepoint together are presented in Table S10 and Figures S10 and S11. No significant differences between the two groups at 1-month post-randomisation were identified (Table 2).

Cost-effectiveness analysis

Thoracic ultrasound-guided care generated non-statistically significant mean healthcare cost savings of £508 (95% CI: -1,567 to 514) and, after including informal care, total care cost savings of £1,393 (95% CI: -3,234 to 528– Table 3). For the cost-effectiveness analysis, even though not statistically significant and nearly identical, standard care generated a higher number of QALYs than TUS-guided care. As a result, we assessed the cost-effectiveness of standard care when compared to TUS-guided care. From a healthcare perspective, the incremental cost-effectiveness ratio of providing standard care was over £583,000 per QALY gained when compared to TUS-guided care, exceeding current UK cost-effectiveness thresholds. Thus, the probability of TUS being cost-effective at a £20,000 per QALY threshold was 0.78. Including the costs of informal care, when compared to TUS, the incremental cost-

effectiveness ratio of providing standard care was over £1.6 million per QALY gained, exceeding

current cost-effectiveness thresholds. Thus, the probability of TUS being cost-effective at a £20,000

per QALY threshold was 0.89.

Discussion

The results of this randomised trial demonstrate that use of TUS in comparison to standard care leads to a statistically significant reduction in duration of hospital stay (primary outcome) without reducing the success rate of pleurodesis in patients with MPE. Symptoms, quality-of-life scores and costs were not significantly different, however, given that the cost-effectiveness analyses took into account the joint uncertainty around cost and effect differences between the two groups[23], we demonstrated that TUS is cost-effective when compared to standard care. Statistically significant improvement in quality-of-life scores at 3 months was noted in the TUS-guided care group, but from a clinical point of view and given the nature of the intervention, this is unlikely to be clinically relevant.

Ultrasound has been demonstrated to enable identification of pleural adhesion in patients undergoing thoracic surgery[24], implying that TUS can confirm the occurrence of pleurodesis. The data from our study confirms pilot data which suggested that early adherence identified by TUS predicts successful pleurodesis at one month in patients with MPE, with excellent inter-rater agreement for TUS-assessed pleural adherence score[16]. Besides being almost universally available in respiratory departments, TUS represents an attractive point-of-care imaging modality that is low cost and radiation-free[25], and is considered standard practice prior to pleural procedures[26,27].

The results of this trial are in line with the results of a recently completed trial of talc pleurodesis in patients with MPE where the success rate at three months was around 70% and the median length of hospital stay (with standard care) was three days[21]. Our study demonstrated that using TUS to guide the timing of talc treatment and when to remove chest tubes shortens hospital admission by one day of the total length of stay, with no reduction in pleurodesis success. It could be argued that more frequent monitoring of fluid output (e.g. every 12 hours) might have led to reduction in the difference in the time to chest tube removal. However, the assessments in this pragmatic trial were planned to occur once every 24 hours to simulate clinical practice. These findings suggest a need for revision of current international treatment guidelines that recommend monitoring fluid output to determine suitability of removing chest tubes and discharging patients, while at the same time acknowledging

that the grade of evidence behind this recommendation is low[6]. The only trial[28] that attempted to prove that expedited chest tube removal (within 24 hours from applying talc) is as effective as waiting for 72 hours was a negative superiority trial which significantly under-recruited (i.e. with the distinct likelihood of a false negative). This is unlike the current study which was adequately powered and demonstrated non-inferiority of a TUS-guided approached in terms of pleurodesis success with the advantage of a shorter length of hospital stay.

The recently published American[7] and European[2] guidelines for managing symptomatic MPE favour the option of inserting IPCs for long-term fluid control for patients who prefer a shorter hospital stay . while recognising the associated risks with IPCs such as chest wall cellulitis[7] and catheter tract metastasis[29]. Up to 8.5% of IPCs are removed prematurely due to complications[2]. The expedited hospital discharge with a TUS-guided approach for pleurodesis may encourage clinicians and patients who are deterred by the need for hospital admission with pleurodesis to re-consider talc treatment in the light of this new data. This is particularly relevant for the subset of patients who do not wish to leave hospital with a medical device in situ. The subset of patients who fail pleurodesis can still be offered IPC insertion if needed thereafter. It has been shown that prior unsuccessful talc pleurodesis does not increase the risk of non-drainage from a subsequently inserted IPC[30],

The main limitation of the TUS-guided approach is that the examination is potentially time consuming for clinicians. In addition, a certain level of expertise is needed to be able to identify different patterns of lung sliding on TUS. This study recruited from both non-specialist and university-affiliated hospitals, and it is reassuring that the treatment effect of using TUS was consistent across recruiting centres whether they offered a specialist pleural service or not. A limitation of the trial was its open-label design; however this was mitigated with the use of standard criteria to enable discharge, and thus the primary outcome measure is likely robust. The shortening in the time to chest tube removal also supports that the reduction in the primary outcome measure (length of hospital stay) is genuine. The trial managed to recruit 90% of the targeted sample size (311 of 344 participants), but this reduction in sample size did not negatively affect the result of the primary outcome.

Conclusion

The use of TUS to guide talc pleurodesis in patients with MPE leads to a shorter duration of hospital stay and is highly cost-effective in comparison to standard care. The reduction in hospital stay associated with TUS does not compromise efficacy of pleurodesis and does not lead to worsened patient symptoms or quality of life. Based on these data, TUS-guidance should now be considered to replace the current standard of care for patients undergoing pleurodesis for MPE.

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Tables

Table 1: Baseline characteristics according to treatment groups

Characteristics	Ultrasound-guided (n=159)	Standard care (n=154)
Gender[1]		
Male	85 (53.5%)	80 (51.9%)
Female	74 (46.5%)	74 (48.1%)
WHO performance status[1]		
0	19 (11.9%)	17 (11.0%)
1	81 (50.9%)	75 (48.7%)
2	44 (27.7%)	46 (29.9%)
3	15 (9.4%)	15 (9.7%)
Missing	0 (0.0%)	1 (0.6%)
Primary cancer type[1]		
Mesothelioma	37 (23.3%)	39 (25.3%)
Lung	34 (21.4%)	41 (26.6%)
Breast	31 (19.5%)	24 (15.6%)
Gastrointestinal	13 (8.2%)	9 (5.8%)
Unknown primary	9 (5.7%)	13 (8.4%)
Gynaecological	11 (6.9%)	10 (6.5%)
Urologic	6 (3.8%)	7 (4.5%)
Other	18 (11.3%)	11 (7.1%)
Blood results[2]		
Haemoglobin (g/dl)	12.9 (11.4, 14.2), 147	12.9 (11.0, 14.3), 142
CRP (mg/L)	28.4 (9.8, 73.2), 120	27.5 (10.0, 71.0), 118
LENT score[1]		
Low 0-1	33 (20.8%)	22 (14.3%)
Moderate 2-4	103 (64.8%)	109 (70.8%)
High risk 5-7	23 (14.5%)	23 (14.9%)
Tube size[1]		
12F or less	66 (41.5%)	63 (40.9%)
16F-18F	11 (6.9%)	14 (9.1%)
20F or more	81 (50.9%)	76 (49.4%)
Missing	1 (0.6%)	1 (0.6%)
Pleural fluid appearance[1, 3]		
Blood stained	72 (45.3%)	70 (45.5%)
Clear	78 (49.1%)	78 (50.6%)
Turbid	6 (3.8%)	5 (3.2%)
Other	2 (1.3%)	1 (0.6%)
Talc type[1]		
Talc poudrage	77 (48.4%)	76 (49.4%)
Talc slurry	82 (51.6%)	78 (50.6%)
Time from randomisation to pleurodesis (days)[2]		
Overall	0 (0, 1), 148	0 (0, 2), 142
Talc poudrage	0 (0, 0), 74	0 (0, 0), 72
Talc slurry	1 (1, 1), 74	2 (1, 3), 70
Trapped Lung[1]		
Yes	29 (18.2%)	26 (16.4%)
No	123 (77.4%)	122 (76.7%)
Missing	7 (4.4%)	6 (3.8%)
EQ-5D utility[4,5]	0.55 (0.26), 157	0.54 (0.29), 152

EQ-5D VAS[4, 6]	54.16 (25.65), 157	55.49 (24.74), 153
VAS chest pain score[2, 7]	4.2 (1.0, 31.5), 153	8.5 (1.0, 32.0), 150
VAS dyspnoea score[2, 7]	45.0 (14.0, 72.5), 153	40.5 (10.0, 65.0), 150

[1] *n (%)*

[2] *median (IQR), n*

[3] *pleural fluid can have more than one of the characteristics*

[4] *mean (SD), n*

[5] *EQ-5D utility scores range from -0.594 to 1, with 1 representing perfect health and 0 equivalent to death.*

[6] *EQ-5D VAS scores range from 0 to 100 with higher scores indicating better quality of life.*

[7] *Chest pain and dyspnoea VAS scores range from 0 (no pain at all) to 100 (worst possible pain).*

Table 2: Primary and secondary outcomes in the treatment groups

	Ultrasound-guided		Standard care			
	Number analysed	**Results**	**Number analysed**	**Results**	**Diff (95% CI)**	**p-value**
Primary outcome (length of hospital stay) days						
Unadjusted, ITT[1,2]	149	2 (2, 4), 3.5 (4.3)	148	3 (2, 5), 4.5 (4.3)	1 (1, 1)	<0.001
Unadjusted, PP[1,2]	129	2 (2, 3), 3.1 (3.0)	139	3 (2, 5), 4.3 (4.1)	1 (0, 1)	<0.001
Adjusted, ITT[3,4,5]	149	0.96 (0.95)	148	1.28 (0.93)	-0.32 (-0.47, -0.18)	<0.001
Secondary outcomes						
Pleurodesis failure at 3 months						
PP[6]	91	27 (29.7%)	109	34 (31.2%)	-1.5% (-10.2%, 7.2%)	
ITT[6]	107	37 (34.6%)	115	37 (32.2%)	3.2% (-6.1%, 12.6%)	
Time to chest tube removal, days						
ITT[5]	154	2.4 (2.5)	152	3.1 (2.0)	-0.72 (-1.22, -0.21)	0.006
PP [5]	129	2.3 (1.5)	139	3.1 (1.9)	-0.84 (-1.25, -0.43)	<0.001
Mixed model[3,5]	154	2.5 (2.59)	152	3.17 (2.57)	-0.67 (-1.16, -0.18)	0.008
EQ-5D utility						
1-month[5,7]	117	0.51 (0.33)	118	0.55 (0.32)	-0.06 (-0.13, 0.01)	0.08
3-month[5,7]	121	0.40 (0.38)	114	0.38 (0.27)	-0.00 (-0.08, 0.07)	0.92
EQ-5D VAS						
1-month [5,8]	99	62.78 (22.49)	106	61.13 (21.25)	1.48 (-5.17, 8.13)	0.66
3-month [5,8]	69	70.87 (18.97)	72	63.10 (22.27)	5.12 (0.40, 9.83)	0.03
VAS chest pain						
1-month [9,10]	99	4 (0.5, 16)	102	2.375 (1, 13)	1.41 (-4.19, 7.01)	0.62
VAS dyspnoea						
1-month[9,10]	99	13.75 (3.5, 43)	102	19.625 (5, 49)	-5.05 (-12.67, 2.57)	0.19

ITT = Intention-to-treat population; PP = Per-Protocol population; VAS = visual analogue scale

Table 3. Total costs, QALYs and cost-effectiveness

|	Standard care Mean (95% CI)	Ultrasound-guided care Mean (95% CI)	Difference Mean (95% CI)
Healthcare costs	£8,150 (7,396-8,925)	£7,642 (6,946-8,350)	-£508 (-1,567 to 514)
Overall care costs	£12,062 (10,722-13,498)	£10,700 (9,458-11,970)	-£1,393 (-3,234 to 528)
QALYs	0.129 (0.118-0.139)	0.128 (0.120-0.139)	-0.001 (-0.015 to 0.014)
Healthcare – ICER*			£583,975
Probability ultrasound cost-effective			0.78
Overall care – ICER*			£1,601,333
Probability ultrasound cost-effective			0.89

Costs are in GB£ *ICER: Incremental cost per QALY gained when standard care was compared to ultrasound-guided care
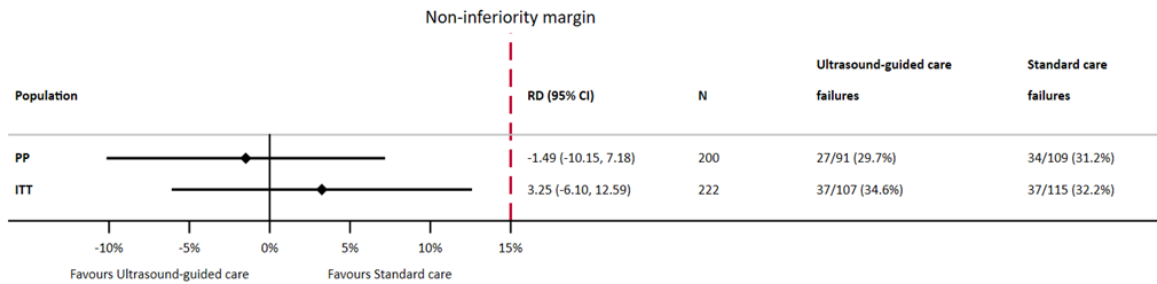
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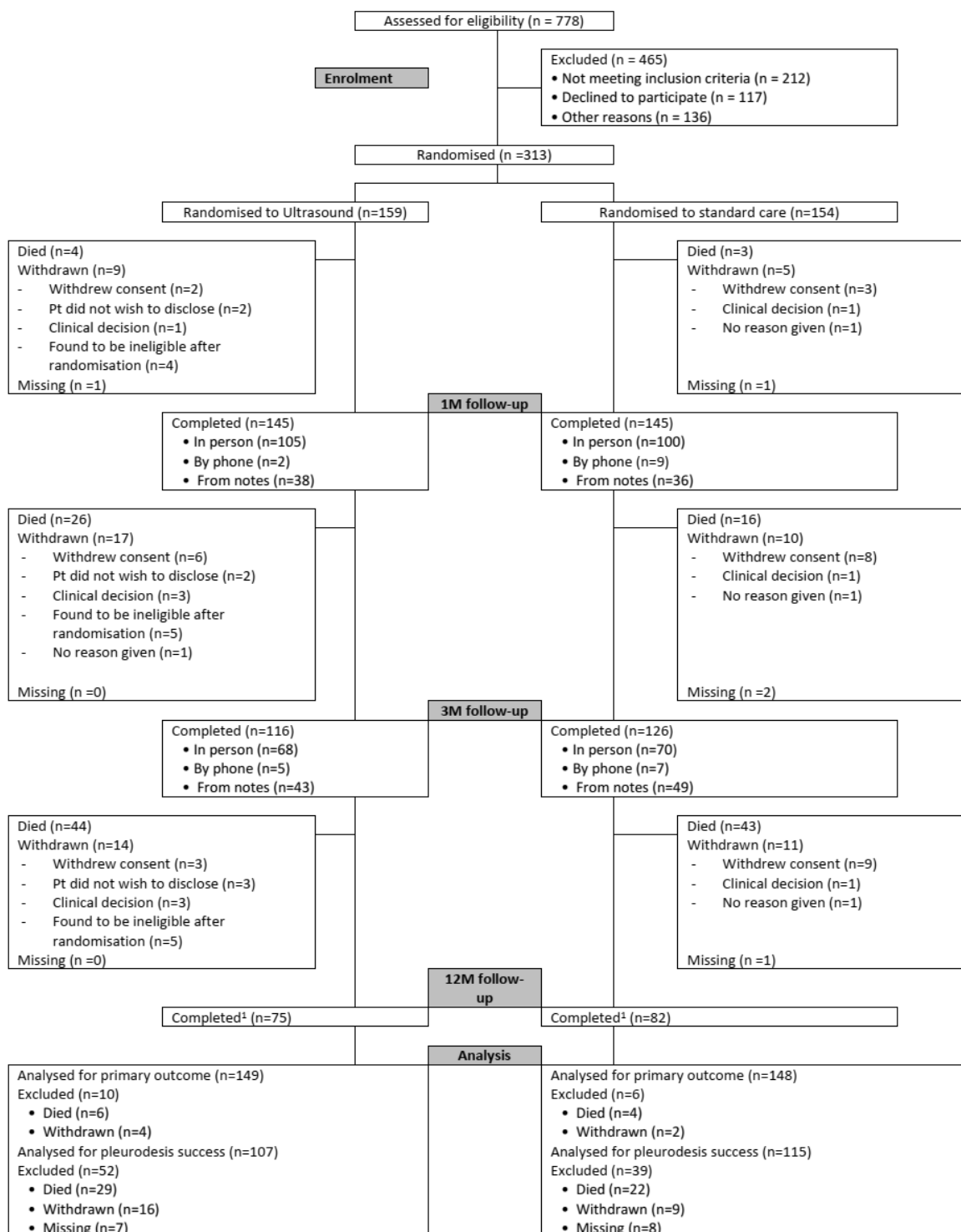
Figure 1: CONSORT flow diagram of trial participants.

[1] Not all participants in the trial reached their 12-month follow-up timepoint prior to the end of trial follow-up.
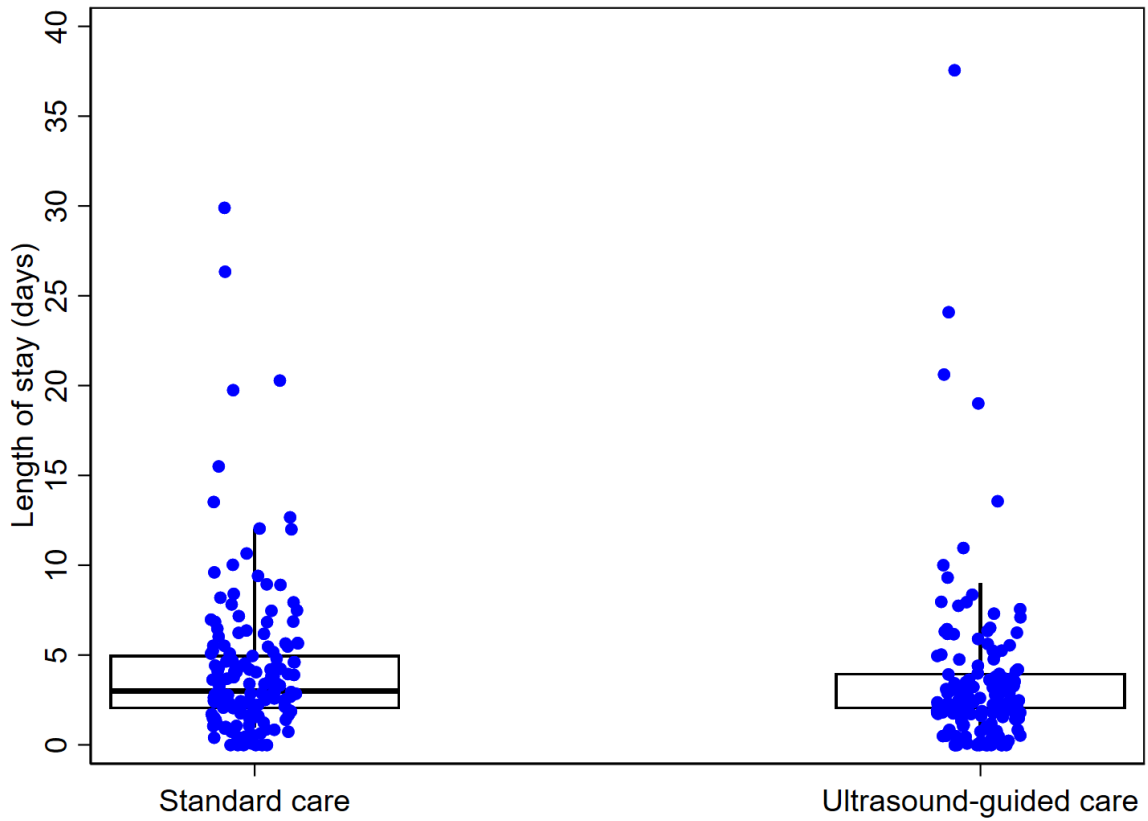
Figure 2: Length of hospital stay in days in the two study groups.

Figure 3: Pleurodesis failure risk differences (with 95% CIs) for the per protocol (PP) and intention to treat (ITT) populations

Note: a non-inferiority margin of 15% was pre-defined and is indicated on the graph