# Medical thoracoscopy with talc poudrage and indwelling pleural catheter insertion versus medical thoracoscopy with talc poudrage alone for patients with symptomatic malignant pleural effusion (TACTIC): a randomised, controlled phase 3 trial

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## Summary

**Background** Patients with suspected malignant pleural effusions (MPE) are often in need of both a confirmatory diagnosis and symptom control. Therapeutic options include talc pleurodesis via chest drain, poudrage during medical thoracoscopy, or alternatively an indwelling pleural catheter (IPC). Combining the diagnostic and therapeutic efficacy of medical thoracoscopy and poudrage with the ambulatory benefits of an IPC has not been studied within a randomised controlled trial. The aim of the TACTIC trial was to determine whether this approach resulted in a reduced length of hospital stay and improvements in dyspnoea.

**Methods** This unblinded, phase 3, randomised controlled trial was undertaken in 11 UK hospitals. Patients with MPE and confirmed malignancy (during medical thoracoscopy or beforehand) received talc poudrage and were randomly assigned by a centralised web-based system to an IPC at the time of medical thoracoscopy or usual care (ie, medical thoracoscopy, poudrage, and admission with large bore tube). Co-primary outcomes were time in hospital (including initial admission for trial procedure and any subsequent readmissions over 4 weeks post procedure) and average breathlessness assessed with visual analogue scale dyspnoea scores, measuring severity of dyspnoea from 0 mm to 100 mm, over a 4-week period. All randomised patients in whom an outcome was available were included in the analysis on a modified intention-to-treat basis. TACTIC was registered with ISRCTN on Aug 8, 2021 (ISRCTN11058680).

**Findings** Participants were recruited from between Dec 15, 2021, and Jan 3, 2024. 124 participants were randomised: 62 to the intervention and 62 to standard care. Leading diagnoses were pleural mesothelioma (46%), lung cancer (28%), and breast cancer (10%). Co-primary outcome data were available for 102 patients for total length of hospital stay (52 in intervention group *vs* 50 in standard care group) and 108 patients for breathlessness (57 *vs* 51). Median time in hospital was 1 day (IQR 1–3, 95% CI 1–2) in the intervention group versus 2 days (IQR 1–3, 95% CI 1–2) in standard care group (p=0·26). Median visual analogue scale dyspnoea scores did not differ between groups: 14·0 mm (IQR 8·8–32·4) in the intervention group versus 19·6 mm (8·1–38·7) in standard care group (p=0·26). Participants in the intervention group required fewer additional invasive pleural procedures by 12 weeks (two [3%] of 60 *vs* 19 [34%] of 56, p<0·0001) Trial related adverse events rates were similar in both groups (46 [74%] of 62 *vs* 44 [71%] of 62, p=0·84). Three related serious adverse events were recorded, all occurring in the intervention group.

**Interpretation** The combination of medical thoracoscopy, poudrage, and IPC did not result in shorter hospital stay but was safe and resulted in similar dyspnoea control compared with standard care. For patients with symptomatic MPE undergoing medical thoracoscopy for pleurodesis who prioritise minimising the length of hospital stay or the need for further invasive pleural procedures, the addition of an IPC alongside poudrage might help to achieve this goal.

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## Introduction

Malignant pleural effusions (MPE) are a common complication of cancer with an estimated global incidence of 70 per 100 000.[1] MPEs pose a substantial burden of disease to patients and health-care systems alike.[2] Patients are often in need of both a diagnosis and symptom control at index presentation, and survival is known to be poor.[3] In the absence of targeted treatments

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## Research in context

### Evidence before this study

We searched PubMed and Embase from database inception to Jan 1, 2024, with the following terms: ('Pleural Effusion, Malignant' OR 'malignant pleural effusion' OR 'MPE') AND ('indwelling pleural catheter' OR 'IPC' OR 'tunneled pleural catheter') AND ('pleurodesis' OR 'talc pleurodesis' OR 'talc poudrage' OR 'medical thoracoscopy' OR 'MT') AND ('randomised controlled trial' OR 'RCT' OR 'observational study' OR 'case series'). We applied filters for humans and English-language publications only. Our search identified multiple randomised controlled trials (RCTs) comparing IPC versus talc pleurodesis in malignant pleural effusion but found no RCTs combining talc poudrage at medical thoracoscopy with IPC insertion versus without. Five retrospective observational studies were identified, reporting pleurodesis success rates of up to 92% and median indwelling pleural catheter removal within as little as 6 days with the use of this combined approach.

### Added value of this study

In this first RCT to apply this procedural approach, pleurodesis at 12 weeks was achieved in just 53% of patients with a median time of IPC removal of 42 days, which differs from the findings reported in the previous observational studies. However, the novel approach was safe and associated with reduced hospitalisation for repeat pleural procedures.

### Implications of all the available evidence

The addition of an IPC to medical thoracoscopy and talc poudrage might be valuable for patients with MPE for whom a key priority is to avoid any further hospitalisation for invasive pleural intervention. However, patients must be counselled that the IPC might be a lifelong intervention, with only half of participants achieving removal by 12 weeks.

to eliminate effusion formation, beyond systemic anticancer therapies, current management strategies aim to reduce symptom burden through pleural intervention.

The initial step of diagnosing an MPE typically includes pleural fluid cytological analysis. However, the overall sensitivity of this test is only 58% and therefore many patients will require a definitive thoracoscopic pleural biopsy.[4] Medical thoracoscopy with pleural biopsies is a combined diagnostic and therapeutic intervention that has an overall sensitivity of more than 95%.[3] Talc poudrage at the time of medical thoracoscopy has a 22% pleurodesis failure rate, but often necessitates a 5-day hospital stay.[5] Indwelling pleural catheters (IPC), inserted as a day-case procedure, provide an alternative strategy to pleurodesis. However, IPCs are often a lifelong intervention and patients and carers might bear the burden of domiciliary drainage and complications including infection.[6–8] Combining the diagnostic and therapeutic efficacy of medical thoracoscopy and talc poudrage with the potential for ambulatory discharge offered by an IPC is therefore an attractive prospect. As an added advantage, should pleurodesis not succeed, the IPC allows continued symptom management without additional invasive pleural intervention.

Retrospective observational data have suggested that a procedure combining medical thoracoscopy, talc poudrage, and IPC insertion might offer high rates of pleurodesis success.[9–13] However, evidence supporting this procedure is restricted to single centre, non-comparative, selective case series. No randomised controlled trial has established the advantages of this approach in comparison with standard care.

The aim of the randomised thoracoscopic talc poudrage and indwelling pleural catheter versus thoracoscopic talc poudrage in malignant pleural effusion RCT (TACTIC) study was to determine whether a combined procedure of medical thoracoscopy, talc poudrage, and IPC insertion might reduce time in hospital and offer improved breathlessness control over 4 weeks after the procedure compared with medical thoracoscopy and talc poudrage alone.

## Methods

### Study design

TACTIC was an unblinded, non-commercial, multicentre RCT based in secondary and tertiary care hospitals in the UK. Patients were recruited from 11 centres with established thoracoscopy and IPC services. Ethical approval was granted by the London-Brent Research Ethics Committee (reference 21/LO/0495). The study protocol has been published previously.[14] This study is registered with ISRCTN (ISRCTN11058680).

### Participants

Patients were eligible if they had a symptomatic pleural effusion and confirmed malignant disease—either a previously confirmed diagnosis by cytology or histology or if frank malignant change was confirmed on visual inspection of the pleura at medical thoracoscopy during study entry.

Inclusion criteria were symptomatic pleural effusion and any of: thoracoscopically confirmed evidence of malignant pleural disease (ie, visible cancer at thoracoscopy, at the point of trial entry), which requires talc poudrage as part of routine clinical care; an established diagnosis of MPE (via biopsy or cytology), which requires drainage and pleurodesis as per standard care, when the patient and operator opt for thoracoscopic talc poudrage; and symptomatic pleural effusion requiring drainage and pleurodesis in the context of

known metastatic disease, when establishing a tissue diagnosis of MPE is not necessary and the patient and operator opt for thoracoscopic talc poudrage.

Exclusion criteria were: technically unable to undergo medical thoracoscopy and talc poudrage (eg, decompensated respiratory failure, uncorrectable clotting, unable to tolerate position, significant suspicion of underlying trapped lung or poor performance status); visual impairment (precluding use of symptom measurement tools); previous talc pleurodesis within the past 3 months on ipsilateral side; no means of telephone contact; younger than 18 years; people who are pregnant or lactating; and people unable to consent to trial participation. All patients provided written, informed consent.

### Randomisation and masking

Eligible patients were randomly assigned on a 1:1 basis to receive the trial intervention (medical thoracoscopy with talc poudrage and IPC insertion) or standard care (medical thoracoscopy with talc poudrage only) with the use of a centralised web-based system (Sealed Envelope, 2024). Minimisation with a random component of 0·85 for cancer type (ie, pleural mesothelioma, cancer other than pleural mesothelioma, or unknown) and WHO performance status at time of trial procedure (0–1 or ≥2) was used. Masking was not feasible given that patients in the intervention group were discharged with an IPC in place. See appendix (p 2) for an outline of randomisation, trial procedure, and follow-up.

### Procedures

All patients underwent medical thoracoscopy and talc poudrage with 3–4 g sterile graded talc, performed according to local practice but consistent with British Thoracic Society guidelines.[3] Patients randomly assigned to the intervention group received an IPC during medical thoracoscopy.

In the standard care group, patients were treated with talc poudrage and admitted to hospital after the procedure as per standard care for 48–72 h and discharged at the discretion of the treating clinician. Patients receiving an IPC could be assessed for discharge on the same day as the intervention, following prespecified discharge criteria (appendix p 4).

All participants were given paper diaries to capture visual analogue scale (VAS) scores for breathlessness and chest pain, with 0 mm anchored to minimal symptoms and 100 mm anchored to worst possible symptoms. Participants recorded their symptoms twice weekly over 4 weeks after the procedure, in addition to interaction with health-care providers.

All patients were followed up for 12 weeks after the trial procedure, or until death. Face-to-face visits were held at 2 weeks (±3 days), 4 weeks (±3 days), and 12 weeks (±7 days) after randomisation. At each follow-up visit, participants underwent standard clinical assessment, chest x-ray, and when possible, thoracic ultrasound. Quality of life questionnaires (EQ5D5L and EORTC QLQc30) were completed at 4 weeks and 12 weeks after the procedure. Adverse events were recorded at all visits. See appendix (pp 3–4) for further information on procedural approach and aftercare.

### Outcomes

The study had two co-primary outcomes: (1) total length of stay in hospital measured in days (including any initial post-procedure hospital admission and subsequent re-admissions, with an overnight admission or continuous period in hospital of >12 h constituting 1 day) over 4 weeks after the procedure; and (2) average breathlessness assessed with the use of a 100 mm VAS dyspnoea (VASd) scale recorded twice weekly over 4 weeks after the procedure. Patient-reported VAS scores were measured independently by two local investigators per site and uploaded to the trial database. Scores were averaged and measurements repeated if they differed by 2 mm or more.

Secondary outcomes were: average chest pain score over 4 weeks after the procedure measured with the use of a 100 mm chest pain VAS scale; total number of days spent in hospital over 12 weeks after the procedure; total number of days until medically appropriate for discharge according to the suggested discharge criteria outlined in a trial specific procedure; and pleurodesis success at 4 weeks and at 12 weeks after the procedure. Pleurodesis was defined as the absence of pleural effusion occupying at least a third of the hemithorax on chest x-ray or more than two rib spaces and 4 cm depth on ultrasound plus no clinical need for further pleural procedure. For patients with an IPC, pleurodesis was defined as output of 50 mL or less on three consecutive drainages within the 12-week trial follow-up period. If a patient died during the trial follow-up period, without evidence of pleurodesis failure, their case was counted as pleurodesis success. Pleurodesis failure was recorded if any of the following procedures were required during the trial follow-up period: therapeutic thoracentesis, chest drain insertion, IPC insertion, or thoracoscopy (either medical or surgical). Secondary measures also included: health-care resource use measured as the number of contacts with health professionals over the 12-week follow-up period; health-related quality of life measured with the use of the EQ5D-5L and EORTC QLQ 30, with responses to EQ-5D converted into utility scores with the use of the current value set for England; and cost-effectiveness of the interventions.

Carer burden was assessed as an optional aspect of the trial, with the use of questionnaires (Short Form 36 [SF36] questionnaire, a five-item carer burden scale, and Work Productivity, and Activity Impairment questionnaire as adapted for caregiving [WPAI CG]). Semi-structured qualitative interviews were also offered to patients and carers to explore the effect, burden, and benefits of interventions.

See Online for appendix

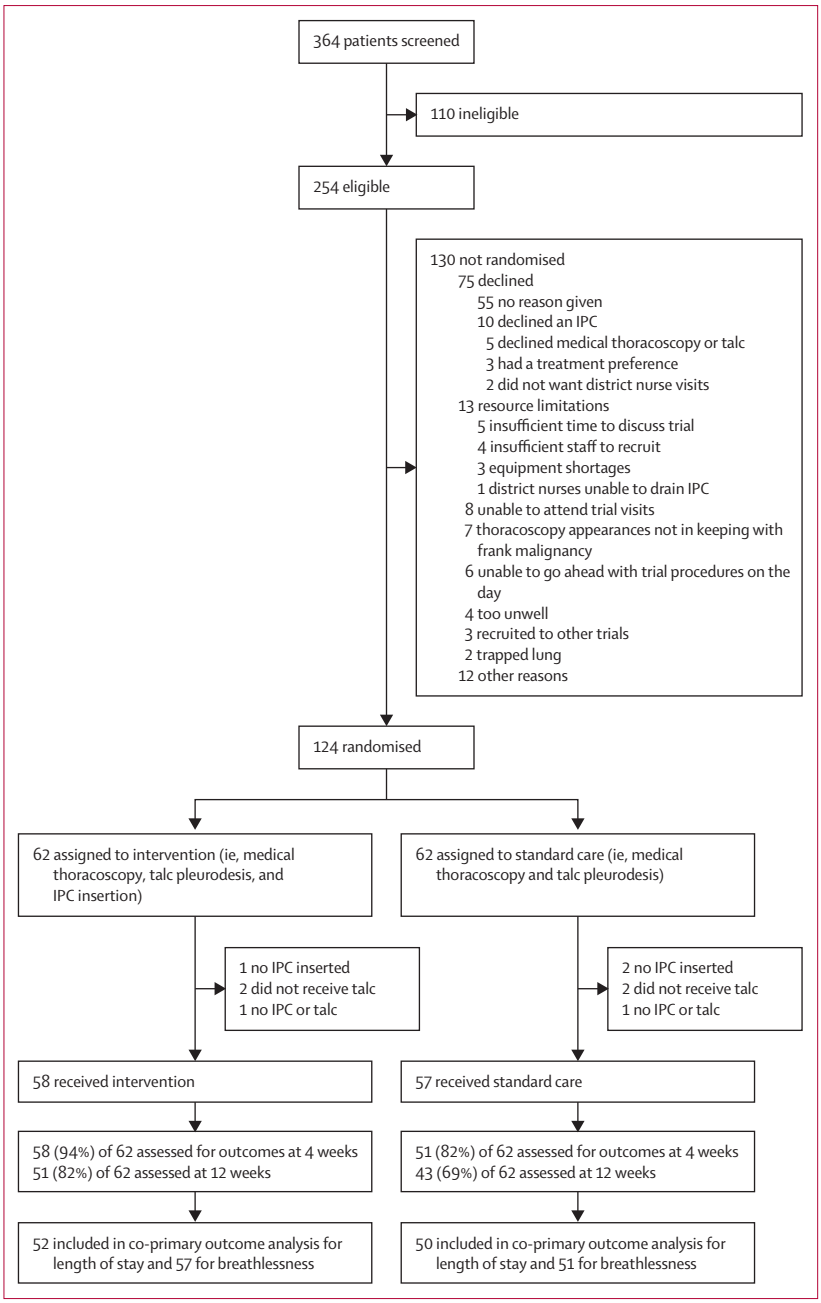


***Figure 1:*** **Trial profile**
IPC=indwelling pleural catheter.

Adverse events were recorded at each trial visit (appendix p 4).

### Statistical analysis

Separate sample size calculations were done for each co-primary outcome. On the basis of findings from previous studies, we assumed a mean hospital stay over 4 weeks of 1 day for patients undergoing medical thoracoscopy, talc poudrage, and IPC insertion, and 3 days for medical thoracoscopy and talc poudrage alone, with a shared SD of 3 days.[15] With the use of these assumptions to detect a difference of 2 days over 4 weeks, with 95% power, a 5% significance level, and 5% loss to follow-up, 124 participants were required.

Previous RCTs have shown that mean VASd score in patients after treatment over 6 weeks is 25 mm (SD 26) when treated with either talc or IPC.[15] The minimal clinically importance difference (MCID) for VASd is 19 mm.[16] To detect a difference of 16 mm, smaller than the MCID to be conservative, with 90% power, 5% significance, and 5% loss to follow up, a total of 116 participants were required. The planned sample size of 124 participants would therefore be overpowered for this outcome.

Data were analysed on a modified intention-to-treat basis with all randomised patients in whom an outcome was available included in the analysis. Analyses were adjusted for minimisation factors (ie, WHO performance status and cancer diagnosis at time of randomisation). We compared the difference between treatment groups in total number of days spent in hospital after the procedure with the use of negative binomial regression with a log link (unadjusted and adjusted by minimisation factors).

Average breathlessness over 4 weeks after the procedure was compared between randomised groups with the use of the Hodges–Lehmann robust estimator (unadjusted) and robust median regression (with adjustment for minimisation factors and baseline breathlessness). No interim analyses were planned or conducted. Analyses were performed with the use of SPSS (version 29.01.0). The complete statistical analysis plan is described within the published trial protocol and in the appendix (pp 5–9).[14]

We undertook a within-trial cost-effectiveness analysis (appendix pp 11–12) comparing the additional cost per quality-adjusted life-year (QALY) gained when combined medical thoracoscopy, talc poudrage, and IPC insertion was compared with medical thoracoscopy and talc poudrage alone. The price year was 2023, and all costs were expressed in pound sterling.

### Role of the funding source

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

## Results

Participants were recruited from 11 UK hospitals between Dec 15, 2021, and Jan 3, 2024. Of 364 participants screened, 254 eligible patients were identified and 124 randomly assigned. 62 patients were assigned to the trial intervention group (medical thoracoscopy, talc poudrage, and IPC insertion) and 62 to the standard care group (medical thoracoscopy and talc poudrage alone). Four patients randomly assigned to the intervention group and five to the standard care group did not receive the trial procedure as assigned. All 124 randomised participants were included in intention-to-treat analyses (figure 1).

Table 1 shows baseline characteristics. Most patients had a WHO performance status of 0 or 1 (99 [80%] of 124). At randomisation, 75 (60%) individuals were undergoing medical thoracoscopy for both diagnosis and pleural effusion management, with pleural biopsies required to confirm histological diagnosis. Cancer diagnosis was subsequently confirmed in 120 (97%) participants. 57 patients (46%) had pleural mesothelioma, 35 (28%) had lung cancer, and 13 (10%) had breast cancer.

Co-primary outcome data were available for 102 patients for total length of hospital stay (including initial admission for trial procedure and any subsequent readmissions over 4 weeks post procedure) and 108 patients for breathlessness (figure 1).

Total length of stay in hospital was a median of 1 day (IQR 1–3, 95% CI 1–2) for patients in the intervention group and 2 days (IQR 1–3, 95% CI 1–2) for those in the standard care group (p=0·26). Adjusted analyses showed no difference in total length of stay after controlling for WHO performance status and cancer type (p=0·67; data not shown).

At 4 weeks after the procedure, median VASd scores did not differ between groups (intervention group median 14·0 mm [IQR 8·8–32·4], n=57 *vs* standard care group 19·6 mm, [8·1–38·7], n=51; p=0·26 unadjusted, p=0·77 adjusted; median difference −3·5 [95% CI −9·56–2·25]; figure 2). Both groups showed a consistent improvement in breathlessness after the procedure, exceeding the published MCID of 19 mm.[16] The intervention group had a median decrease from baseline of 27·4 mm (IQR 5·0–50·4), whereas the standard care group had a decrease of 19·3 mm (10·6–28·9). Longitudinally, there were no between group differences in median VASd or at any specific timepoint (appendix p 16). Controlling for site did not affect either co-primary outcome measure (data not shown).

Several protocol deviations occurred during recruitment if a participant did not undergo their randomised trial intervention (n=9) or did not follow trial protocol for discharge (n=26, appendix p 13). Post-hoc per-protocol analyses were therefore conducted for the primary outcomes. Data were available for 54 (93%) of 58 patients in the intervention group and 24 (71%) of 34 in the control group.

The analysis showed a median total length of hospital stay of 1 day (IQR 1–2, 95% CI 1–2) for the intervention group and 2 days (2–5, 1–2) for the control group (p=0·025 unadjusted, p=0·014 adjusted, appendix p 13) and no difference in breathlessness scores over 4 weeks after procedure (intervention group median 14·1 mm [IQR 9·9–32·4], standard care group 19·6 mm [8·1–46·1], p=0·16 unadjusted, p=0·96 adjusted; appendix p 14).

There were higher chest pain VAS scores in the standard care group on day 1 after procedure (intervention group median 24·7 mm [IQR 5·0–42·0], n=54; standard care arm 36·0 mm [11·5–67·5], n=47; median difference=−10·0 mm [95% CI 0 to −24·5], p=0·041). Pain scores improved over 4 weeks in both groups with no difference between groups recorded at any other timepoint (data not shown).

Total length of hospital stay over 12 weeks did not differ between groups (intervention group median 2 days [IQR 1–4]; standard care group median 2 days [1–6]; p=0·71 unadjusted, p=0·98 adjusted). Total length of stay, not including participants who spent time in hospital after objective discharge criteria were met (n=99)

| | Intervention: medical thoracoscopy with talc poudrage and IPC insertion (n=62) | Standard care: medical thoracoscopy with talc poudrage only (n=62) |
|---|---|---|
| Age, years | 72·6 (9·0) | 71·4 (10·0) |
| Sex | | |
| Female | 20 (32%) | 21 (34%) |
| Male | 42 (68%) | 41 (66%) |
| WHO performance status* | | |
| 0 | 12 (19%) | 11† (18%) |
| 1 | 36 (58%) | 40 (66%) |
| 2 | 10 (16%) | 8 (13%) |
| 3 | 4 (7%) | 2 (3%) |
| Cancer diagnosis at randomisation (minimisation variables) | | |
| Mesothelioma | 8 (13%) | 8 (13%) |
| Cancer other than mesothelioma | 17 (27%) | 16 (26%) |
| Unknown | 37 (60%) | 38 (61%) |
| Final cancer diagnosis | | |
| Lung | 19 (31%) | 16 (26%) |
| Mesothelioma | 31 (50%) | 26 (42%) |
| Breast | 3 (5%) | 10 (16%) |
| Ovarian | 0 (0%) | 1 (1·6%) |
| Lymphoma | 1 (1·6%) | 0 (0%) |
| Upper gastrointestinal tract | 1 (1·6%) | 3 (5%) |
| Other | 5 (8%) | 4 (7%) |
| Unknown | 2 (3%) | 2 (3%) |
| Smoking status | | |
| Current | 8 (13%) | 5 (8%) |
| Ex-smoker | 32 (52%) | 33 (53%) |
| Never-smoker | 22 (35%) | 24 (39%) |
| Side of effusion for trial intervention | | |
| Left | 28 (45%) | 31 (50%) |
| Right | 34 (55%) | 31 (50%) |
| Previous pleural intervention (any) on side of trial intervention | | |
| No | 10 (16%) | 16 (26%) |
| Yes | 53 (84%) | 46 (74%) |
| Previous talc pleurodesis on side of trial procedure, number (%) | 0 (0%) | 1 (1·6%) |
| Trapped lung on post-medical thoracoscopy chest x-ray | | |
| Not trapped | 22‡ (35%) | 19 (31%) |
| Mild (≥50% lung apposition) | 27 (44%) | 30 (48%) |
| Moderate (<50% lung apposition) | 10 (16%) | 8 (13%) |
| Severe (no lung apposition) | 2 (3%) | 5 (8%) |

(Table 1 continues on next page)

| | Intervention: medical thoracoscopy with talc poudrage and IPC insertion (n=62) | Standard care: medical thoracoscopy with talc poudrage only (n=62) |
|---|---|---|
| (Continued from previous page) | | |
| Current anti-cancer treatment (any) | | |
| No | 62 (100%) | 58 (93·5%) |
| Yes | 0 (0%) | 4 (6·5%) |
| Current medications | | |
| Steroids | 3 (5%) | 2 (3%) |
| NSAIDs | 2 (3%) | 1 (1·6%) |
| Pre-medical thoracoscopy VAS dyspnoea, mm§ | 48·5 (23·0–74·5) | 50·2 (22·1–74·0) |
| Pre-medical thoracoscopy VAS chest pain, mm§ | 6·0 (1·0–47·9) | 6·0 (1·0–39·6) |
| EORTC QLQ-C30 summary score | 67·4 (56·2–76·4) | 69·7 (55·3–77·3) |
| EORTC QLQ-C30 global health score | 50 (25–58·3) | 41·7 (33·3–66·7) |
| EQ5D utility score¶ | 0·70 (0·48–0·78) | 0·66 (0·52–0·76) |

Data are mean (SD), number (%), or median (IQR). IPC=indwelling pleural catheter. NSAIDs=non-steroidal anti-inflammatory drugs. VAS=visual analogue scale. *WHO performance status scores range: 0=able to carry out normal activities without restriction; 1=restricted only on strenuous activity; 2=restricted on any work activities but capable of all self-care; 3=symptomatic and in a chair or bed for more than half the day; and 4=confined to chair or bed and unable to carry out any self-care. †Performance status not recorded in one participant. ‡Trapped lung assessment on post-medical thoracoscopy chest x-ray not recorded in one participant. §n=60 in the intervention group and n=60 in the standard care group. ¶n=60 in the intervention group and n=59 in the standard care group.

***Table 1:*** **Baseline characteristics**

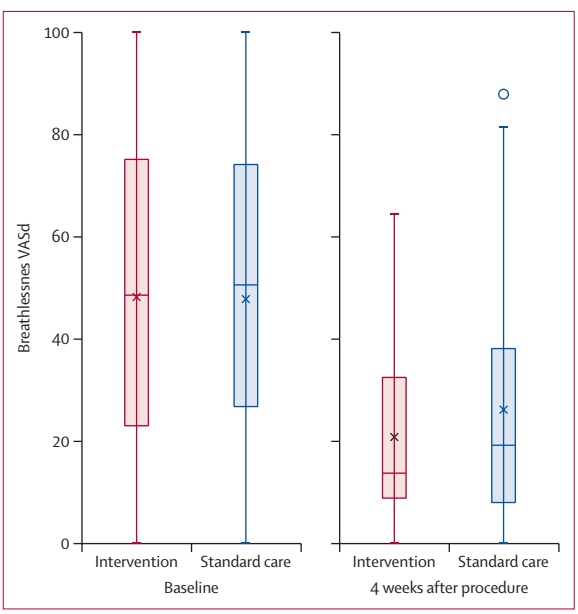


***Figure 2:*** **Box plot of VASd scores in intervention arm versus standard care**
Dyspnoea scores for participants in the intervention group versus standard care group are shown at baseline and then at 4 weeks after the procedure. The box plot shows the median, IQR, and absolute range of the VASd scores. VASd=visual analogue scale dyspnoea.

remained unchanged (median 2 days [IQR 1–4]; p=0·62 unadjusted, p=0·74 adjusted).

Pleurodesis outcome data were available for 100 (81%) participants at 4 weeks and 103 (83%) participants at 12 weeks. Successful pleurodesis, as defined by both radiological and clinical criteria, was achieved at 4 weeks in 21 (40%) of 53 patients in the intervention group and in 19 (40%) of 47 participants in the standard care group (p=0·94). By week 12, 28 (53%) of 53 patients in the intervention group and 21 (42%) of 50 patients in the standard care group had achieved successful pleurodesis (p=0·27). Adjusted analyses, controlling for WHO performance status and pleural mesothelioma diagnosis, showed no between group difference in 12-week pleurodesis success rates (p=0·11; data not shown).

116 (94%) patients had data available on need for repeat invasive pleural intervention for effusion control over 12 weeks. By 12 weeks an additional pleural procedure for fluid control was recorded for two (3%) of 60 patients in the intervention group and 19 (34%) of 56 patients in the standard care group (p<0·0001, appendix pp 17–18). By 12 weeks, 37 (62%) of 60 patients who received an IPC had their device removed. After IPC removal, further pleural intervention was required in two (5%) of 37 individuals (one therapeutic thoracentesis and one repeat IPC insertion), meaning that by 12 weeks, 35 (58%) of 60 individuals had IPCs removed successfully for pleurodesis. Median time to IPC removal was 42 days (95% CI 30–54).

No significant differences were seen across the two groups, including hospital re-admissions, primary care contacts, outpatient and emergency care contacts, and visits to other health-care professionals, between randomisation and follow-up at 12 weeks (appendix pp 28–29).

No significant differences were observed in quality-of-life scores between groups at any timepoint (appendix pp 21–27). At 12 weeks, the median EORTC QLQ-C30 global health score was 66·7 (IQR 50·0–83·3) in the intervention group (n=44) and 62·5 (50·0–75·0) in the standard care group (n=38; p=0·38). Similarly, EQ-5D utility scores did not differ between groups at any timepoint. At 12 weeks, the median EQ-5D score was 0·73 (0·58–0·84) in the intervention group (n=44) and 0·74 (0·64–0·84) in the standard care group (n=39; p=0·45).

The initial cost of the trial intervention exceeded that of standard care by £1406, but subsequent health-care resource use did not differ significantly between groups (appendix p 28). Medical thoracoscopy with talc poudrage and IPC insertion was not considered cost-effective according to current UK thresholds, because the additional cost per QALY gained exceeded the £20 000–30 000 range typically applied and was £178 874.

In the intervention group, 46 participants had a total of 96 adverse events compared with 44 participants with 84 adverse events in the standard care group (table 2). Three related serious adverse events were recorded, all occurring in the intervention group. One patient was admitted to hospital for IPC-related pain, which improved on removal of the device. Two hospital admissions for management of empyema were recorded in the same patient. No deaths were attributable to trial procedures. The proportion of patients having at least

one AE or complication did not differ significantly between groups (p=0·84) and the rate of adverse events did not differ between groups (p=0·41).

13 (11%) of 115 participants who received the trial intervention had missing data for the co-primary outcome of length of stay and seven (6%) participants had missing data for breathlessness. Missing primary outcome data were consistent with missing completely at random and were unrelated to randomised group, minimisation factors, baseline breathlessness, or baseline characteristics including, age, sex, smoking status, or duration of symptoms.

A best-case and worse-case sensitivity analysis was performed for VASd, chest pain, and length of stay (days in hospital within the first 4 weeks), to account for missing data. No sensitivity analyses produced a statistically significant effect favouring standard care for VASd or chest pain. Significantly shorter length of stay was found in the standard care group, only when missing values for the intervention group were imputed at a level of 6 days or more. The opposite result was observed in the intervention group, when the missing values for the standard care group were imputed at a level of 4 days or more. Complete sensitivity analyses are shown in the appendix (p 19).

| | Intervention: medical thoracoscopy with talc poudrage and IPC insertion (n=62) | Standard care: medical thoracoscopy and talc poudrage only (n=62) |
|---|---|---|
| Chest pain requiring analgesia | 38 (56)* | 29 (40) |
| Subcutaneous emphysema | 8 (9) | 10 (13) |
| Hypotension | 6 (6) | 3 (4) |
| Fever | 3 (4) | 2 (3) |
| Post-procedure air leak or pneumothorax | 4 (6) | 8 (11) |
| Pneumonia | 1 (1) | 2 (2) |
| Empyema | 2 (2)† | 1 (1) |
| Subcutaneous infection | 3 (3) | 2 (2) |
| IPC related infection | 3 (3) | NA |
| IPC blockage | 1 (1) | NA |
| Other | 5 (5) | 8 (8) |
| Total | 46‡ (96) | 44‡ (84) |

Numbers in the table listed as the number of participants (number of events). IPC=indwelling pleural catheter. NA=not applicable. *One serious adverse event. †Two serious adverse events, both occurring in the same patient. ‡Participants might have had more than one adverse event.

***Table 2:*** **Adverse events related to trial intervention, including procedural complications**

## Discussion

In the TACTIC trial, patients with symptomatic MPE randomly assigned to medical thoracoscopy with talc poudrage and IPC insertion showed no significant difference in length of hospital stay, dyspnoea control, or chest pain after the procedure compared with patients receiving medical thoracoscopy and talc poudrage alone.

We hypothesised that the addition of an IPC at medical thoracoscopy and talc poudrage might enable earlier hospital discharge after the procedure and reduce the risk of subsequent presentations with pleurodesis failure, thereby reducing overall time spent in hospital. Results from our primary analyses showed that the number of nights spent in hospital (including any initial hospital admission after the procedure and subsequent readmissions) did not differ between groups over 4 weeks. As a result, the additional costs of the intervention (£1406 per patient) were not offset by reductions in other related costs, and the additional cost per QALY gained was above the thresholds typically accepted in the UK, resulting in the IPC addition not being cost effective. The main drivers for the additional costs of the interventions were: the need of follow-up district nurse home visits for monitoring of the IPC, which required an additional 5 h of district nursing time, at a cost of £574; and the costs of the IPC insertion kit and additional drainage and bottles at a total cost of £319.

However, we noted that 26 (42%) of 62 patients randomly assigned to medical thoracoscopy and talc poudrage only were discharged home less than 48 h after procedure (including ten discharged on the same day). This finding conflicted with the trial protocol, which advised hospital admission for continuous chest tube drainage for a minimum of 48 h. It is probable that trial recruitment in the immediate post-COVID-19 era contributed to this finding. At the height of the pandemic, UK national guidance advised against admission for talc pleurodesis. We addressed this breach of protocol with post-hoc per protocol analyses, excluding patients discharged in less than 48 h after the procedure. Although these findings are limited by the smaller number of included patients, we observed with interest that length of stay was reduced by 2 days in the combined procedure group compared with individuals receiving conventional medical thoracoscopy and talc poudrage.

For more on **pleural services during the COVID-19 pandemic** see https://wmcanceralliance.nhs.uk/images/Documents/Covid-19_2020/Pleural_services_during_COVID-19_pandemic.pdf

With the IPC in place as a backup if talc pleurodesis fails, we expected that post-procedure breathlessness scores might reflect improved symptom control with the combined procedure. However, our results showed no significant between-group difference in post-procedure VASd scores. This result is consistent with findings from previous trials of interventions for MPE.[5,17,18] However, both groups reported significant and clinically meaningful breathlessness improvement after the procedure, with a reduction in mean VASd scores over 4 weeks exceeding the MCID of 19 mm.[16] This finding should provide confidence for clinicians and patients to base their choice of intervention for MPE control on individualised priorities (ie, including a preference to avoid repeat hospital attendances or further invasive pleural procedures) in the knowledge that both interventions appear to offer effective symptom control.

In previous observational case series, Reddy and colleagues[9] reported a median time to IPC removal of 7·5 days and Boujaoude and colleagues[10] reported a median time of 6 days[10] with the combined procedure incorporating daily IPC drainage. The authors of these

studies assert that in comparison with conventional IPC use (with median time to IPC removal of 56 days reported before these series[19]), this approach has potential to offer rapid pleurodesis. Results from our TACTIC RCT do not support this statement, with only 35 (58%) of 60 successful IPC removals by 12 weeks (and not requiring re-intervention) and median time to IPC removal of 42 days (95% CI 30–54). Procedural differences might partly account for this discrepancy, with large bore chest drains remaining on suction for 24 h and a more intensive regimen of IPC drainages used by Reddy and colleagues.[9] Aligned with our findings, the ASAP randomised controlled trial[20] reported a median time to auto-pleurodesis with daily IPC drainage of 54 days (95% CI 34–83). In the IPC plus study,[21] delivery of talc slurry via IPC resulted in 35 (51%) of 69 patients achieving a successful pleurodesis at day 70.

Overall pleurodesis success rates in the TACTIC randomised controlled trial are lower than reported in previously published literature, with 21 (42%) of 50 patients undergoing conventional medical thoracoscopy and talc poudrage achieving successful pleurodesis by week 12 compared with 125 (78%) of 161 reported in the TAPPS trial.[5] Although the TACTIC RCT was not designed to evaluate pleurodesis success, it is likely that the strict protocol definition of pleurodesis success affected these findings. When the need for further pleural intervention for symptomatic effusion recurrence is considered, which is likely a more meaningful outcome for patients and is in-keeping with the definition used in the IPC-PLUS study,[21] higher success rates are noted. The reduced risk of repeat pleural intervention with use of an IPC is in-keeping with previous literature.[22]

A final diagnosis of pleural mesothelioma was recorded in 57 (46%) of 124 patients. This finding is higher than that in previous observational studies on the combined procedure; two (7%) of 30 patients in Reddy and colleagues' study[9] and three (10%) of 29 in Boujaoude and colleagues' study[10] had a diagnosis of pleural mesothelioma. Although this result might be partly explained by TACTIC being a UK-based MPE study, where historically patients with PM are better represented compared with non-UK based MPE studies,[5,23] the proportion of patients with pleural mesothelioma within TACTIC remains higher than previously described and might represent a shift in UK thoracoscopy practice. A previous UK retrospective analysis[24] of data from the TIME1 randomised controlled trial showed that patients with pleural mesothelioma had a lower rate of pleurodesis success than did patients with other malignancies (73% *vs* 85% success, p=0·02), which might further explain this observation.

To the best of our knowledge TACTIC is the first randomised controlled trial to evaluate a combined procedure with medical thoracoscopy, talc poudrage, and IPC insertion compared with medical thoracoscopy and talc poudrage alone, providing the largest body of evidence to date on this therapeutic approach. Patient-centred co-primary outcome measures were chosen, with input from patient and public involvement members to ensure relevance to the MPE population. Participants were recruited from 11 sites representing a range of UK district general and teaching hospitals. A limitation of this trial is that blinding was not possible due to the nature of the interventions studied, which is inherently subjective and dependent on patients' perception of breathlessness. To mitigate against this risk of bias created by the unblinded design, we incorporated measures in the trial protocol including suggested discharge criteria for patients in both groups and requirement for consultation with independent clinicians masked to group assignment in cases of radiological effusion recurrence when local investigators chose not to intervene with a further procedure.

We noted that 12 (19%) of 62 patients with IPCs were unable to access the minimum of five IPC drainages per week because of UK NHS resource limitations. In view of evidence supporting daily IPC drainage for patients in whom pleurodesis success and early IPC removal is a priority,[20,25] it is essential that UK community health-care teams are adequately financed and resourced to provide this intervention. Understanding whether this observation is representative of a wider mismatch in terms of service demand and provision in the UK is essential to improve the quality of health-care delivery for patients with MPE.

In summary, the TACTIC multicentre UK randomised controlled trial shows that the combination of medical thoracoscopy, talc poudrage, and IPC insertion compared with medical thoracoscopy and talc poudrage alone was safe, caused patients no additional pain, but did not improve dyspnoea control compared with usual care. The trial did not show any difference in the overall length of stay but a post-hoc per-protocol analysis indicates that when compared with conventional medical thoracoscopy and talc poudrage practice with a 48 h hospital admission, the addition of an IPC might reduce length of stay.

Appropriate patient selection for a combined pleural procedure is paramount, and it remains essential to explore individual treatment priorities when clinicians select an intervention for management of MPE. For some patients with symptomatic MPE undergoing medical thoracoscopy for pleurodesis and prioritising minimal further hospital attendances or further invasive pleural interventions, the addition of an IPC alongside talc poudrage might help to achieve this goal.

**Contributors**

MM, NMR, and NM conceived the idea of the study. NMR and NM secured funding from the National Institute for Health and Care Research. AD, AS, EH, JM, AJM, RB, RL-F, RFM, PW, MM, NMR, and NM were part of the trial steering committee and helped design the trial including the methodology and statistical analysis plan. AD, AS, and EH coordinated and delivered the trial. AD, RB, PW, SR, and RL-F verified the data and performed the data analysis. AD, AS, SR, and RL-F wrote the manuscript. AS and NM were responsible for submitting the manuscript. All authors reviewed the data and the data analyses and provided peer-review on the final manuscript.

**Declaration of interests**
RB has received consultancy fees from Rocket Medical. MM has received consultancy and speaker fees from Olympus and Beckton Dickinson. All other authors declare no competing interests.

**Data sharing**
De-identified trial data with data dictionaries can be made available following publication, on request. Please send requests to dm.ortu@ndm.ox.ac.uk; appropriate permissions and data sharing agreements will be required before any transfer of information.

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