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The impact of outpatient vs inpatient management on health-related quality of life outcomes for patients with malignant pleural effusion – the OPTIMUM randomized clinical trial.

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Abstract

Background

The principal aim of malignant pleural effusion (MPE) management is to improve health related quality of life (HRQoL) and symptoms.

Methods

In this open-label randomised controlled trial, patients with symptomatic MPE were randomly assigned to either IPC insertion with the option of talc pleurodesis or chest drain and talc pleurodesis. The primary endpoint was global health status, measured with the EORTC QLQ-C30 questionnaire at 30 days post-intervention. 142 participants were enrolled from July 2015 to December 2019.

Results

Of participants randomly assigned to IPC (n=70) and chest drain (n=72), primary outcome data were available in 58 and 56 patients, respectively. Global health status improved in both groups at day 30 compared to baseline: IPC (mean difference 13.11 *p*=0.001) and chest drain (mean difference 10.11 *p*=0.001). However, there was no significant between-group difference at day 30 (mean inter-group difference in baseline-adjusted global health status of 2.06 ([95% CI -5.86 to 9.99]; p = 0.61), day 60 or day 90. No significant differences were identified between groups in breathlessness and chest pain scores. All chest drain arm patients were admitted (median length of stay 4 days); 7 in the IPC arm required intervention-related hospitalization.

Conclusion

While HRQoL significantly improved in both groups, there were no differences in patient reported global health status at 30 days. The outpatient pathway using an IPC was not superior to inpatient treatment with a chest drain.

Trial Registration

ISRCTN registration:15503522.

Introduction

Malignant pleural effusions (MPE) result in breathlessness, reduced function and impaired health-related quality-of-life (HRQoL), often representing an advanced terminal illness with a median survival of 3-12 months[1].

Two definitive management options for MPE include hospital admission for a chest drain insertion with talc slurry pleurodesis or outpatient ambulatory management with an indwelling pleural catheter (IPC). Over the last decade, IPCs have increasingly become a first-line intervention for MPE with recent advances incorporating talc pleurodesis[2] or a daily drainage strategy[3]. These approaches may stop fluid production via pleural symphysis. However, these two options may exert distinct influences on patients' quality of life. For example, an IPC shifts the burden of care to the community, patient and their carers, and involves a period of repeated drainage and frequent healthcare visits, whilst a chest drain and talc pleurodesis entails a median hospital stay of 4 days[4].

Although improving HRQoL is a central treatment goal, a systematic review has identified limited comparative data on HRQoL outcomes to guide best practice[5]. This trial tests the hypothesis that outpatient management of MPE utilising an IPC with the option of talc pleurodesis improves HRQoL compared to usual inpatient management with a chest drain and talc pleurodesis.

This is the first randomised controlled study to evaluate HRQoL as a primary outcome measure in MPE intervention.

Methods

Trial Design

The Out Patient Talc Slurry via Indwelling Pleural Catheter for Malignant Pleural Effusion Vs Usual Inpatient Management (OPTIMUM) trial is a randomised, two-arm, open-label superiority trial conducted at 11 hospitals in the United Kingdom and one hospital in Australia. UK ethics approval was obtained from the National Research Ethics Service (NRES) Committee South East Coast, Brighton and Sussex (15/LO/1018). For Australia, approval was obtained from the Sir Charles Gairdner Group Human Research Ethics Committee. The trial protocol has been published[6] (Supplement 1).

Participants

All participants were adults diagnosed with MPE made either by histocytological confirmation or clinical and radiological features of metastatic pleural disease in patients with histologically proven primary cancers. Participants were required to have a WHO performance status of two or less, unless a performance status of three was likely to improve with pleural drainage. Participants also needed an expected survival of greater than three months. The exclusion criteria were age less than 18 years old; pregnant or lactating; known allergy to talc or lidocaine; lack of symptomatic relief from effusion drainage; district nurse/carers/hospital team unable to carry out at least twice weekly IPC drainage; underlying lymphoma or small cell carcinoma except if chemotherapy had failed or the patient was to be referred for palliative management; non-malignant effusions; loculated pleural effusion; and patients unable to provide written informed consent to trial participation. Participants were screened from both the outpatient and inpatient setting.

Randomization

Participants were randomised 1:1 to either IPC insertion or chest drain and talc slurry pleurodesis. Permuted block randomisation (block sizes 4, 6, 8) was performed with allocation concealment maintained using a web-based randomisation service (www.sealedenvelope.com). Treatment allocation was unblinded and stratified to the following factors: age (<65 years, ≥65 years), malignancy subtype (lung, mesothelioma, breast, other) and WHO performance status (0, 1, 2, 3). Patient blinding was not practical due to inherent differences between the interventions.

Procedures

Supplementary figures s1-s2 (section 3 in Supplement 2) provides further detail of the trial interventions.

Participants randomised to the IPC group underwent catheter insertion as a day case under local anaesthesia using a percutaneous Seldinger technique. Following insertion, an attempt was made to evacuate the fluid completely, using pleural manometry where available, to enable safe large-volume drainage and reduce the risk of re-expansion pulmonary oedema. Patients then returned after three days for review and a further attempt at maximal pleural fluid drainage. If the fluid removed at this visit averaged less than 150mls/day since IPC insertion and non-expandable lung was ruled out by ultrasound or X-ray, talc pleurodesis was attempted through the IPC. The protocol was amended in October 2016 to remove the <150mls/day drainage criteria as feedback from recruiting centres suggested incomplete drainage at insertion made fluid estimation at the day 4 visit difficult. Four grams of sterile talc was then administered as a slurry (section 1.1.1 in Supplement 2) and participants observed for 1 hour following instillation. Patients or district nurses were advised to perform daily IPC drainages as an 'aggressive' drainage strategy using 1 litre bottles and return at day 7 for review, chest X-ray and repeat drainage. If satisfactory pleural apposition with absence of pleural sliding was seen on ultrasound in 5 of 6 areas (Figure s3 in Supplement 2), repeated drainage was halted. Participants returned on day 14 for review and the IPC removed if pleural apposition was maintained with evidence of minimal fluid on ultrasound.

In cases where talc instillation was either not attempted or in participants that did not meet the criteria for IPC removal at day 14, regular IPC drainage was continued throughout the study follow up period. The frequency of drainage was at the discretion of the treating physician. For these participants, the recommended approach was early assessment in the clinic if they experienced three consecutive drainages of less than 50mls of fluid. If either a chest x-ray or ultrasound showed no significant residual pleural collection, then the IPC could be removed.

Participants randomised to chest drain and talc pleurodesis underwent management as per the 2010 British Thoracic Society (BTS) pleural disease guidelines[7]. A 12F-14F chest drain was inserted using ultrasound guidance under local anaesthesia, and the patient was admitted to hospital. After 24hrs, if the chest X-ray ruled out an non-expandable lung, 4 grams of talc slurry was instilled. The drain was then removed when the pleural fluid output dropped below 250mls/day. Patients with non-expandable lung or any other contraindication to talc slurry pleurodesis (such as an air leak) could be managed using an alternative strategy and continued their follow up in the study.

Follow-up

All participants underwent follow up until 90 days after intervention or death, whichever occurred first. Trial visits were conducted at the outpatient clinic on day 4 for the IPC group and 7, 14, 30, 60 and 90 days after the intervention for both groups. If fluid recurrence or complications developed,

the trial clinicians were permitted to perform further tests and procedures (e.g. IPC insertion or referral for thoracic surgery) as part of usual clinical care.

Outcomes

Primary Outcome

The primary outcome was global health status, at 30 days post-intervention measured with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer 30 (EORTC QLQ C-30). This is a validated, cancer specific, multidimensional instrument that asks participants to report on aspects of their health-related quality of life over the previous week. It is suitable for all cancer diagnoses[8] and can be repeated at frequent intervals to monitor quality of life over time[9].

Secondary Outcomes

Secondary outcomes included global health status at day 60 and day 90 post-intervention, adverse event rates, breathlessness, chest pain scores and pleurodesis failure rate. Pleurodesis failure was defined as chest X-ray opacification greater than 25% on the side of intervention or the need for subsequent pleural intervention on the same side as pleurodesis at 30, 60 and 90 days post-intervention. Breathlessness and chest pain scores at 30, 60 and 90 days post-intervention were measured using the 0-100mm visual analogue scale.

Statistical analysis

Using an analysis of covariance model (ANCOVA), adjusting for baseline global health status, a sample size of 142 (71 vs 71) would detect a clinically significant difference of 8 points in global health status with 80% power and a 5% significance level. This assumes a common standard deviation of 23.6 in Stage III-IV cancer[8]. The covariate has an R-squared of 0.49. An interim analysis was planned once 50% of patients were enrolled to determine if the recruitment target needed amendment.

At this interim analysis, a blinded assessment of data demonstrated a 14% loss to follow-up at 30 days. The trial steering committee agreed that given funding, recruitment rates and the nature of the patient population, increasing the sample size would not be feasible and agreed to continue recruitment until December 2019 to achieve the original trial objective.

Data were analysed on an intention-to-treat basis in all patients in whom outcome data were available. The primary efficacy analysis was based on ANCOVA. Regression analyses were adopted to compare estimates for secondary efficacy analyses.

Data attrition for the complete case analysis prompted a post-hoc sensitivity analysis. Multiple imputation by chained equations was used to impute the missing data[10]. Using mice (Multivariate Imputation by Chained Equations) R package[11], 300 simulated datasets were generated, and an ANCOVA analysis was performed on all of the imputed datasets with the results pooled. All analyses were conducted using R version 4.0. The trial statistical analysis plan is outlined in Supplement 3.

The trial was registered on the ISRCTN registry (Identifier: 15503522).

Results

After screening a total of 548 patients for eligibility, 142 participants were recruited between July 2015 and November 2019. Four patients withdrew, and one died before undergoing the randomised intervention. They were excluded from the analyses (Figure 1).

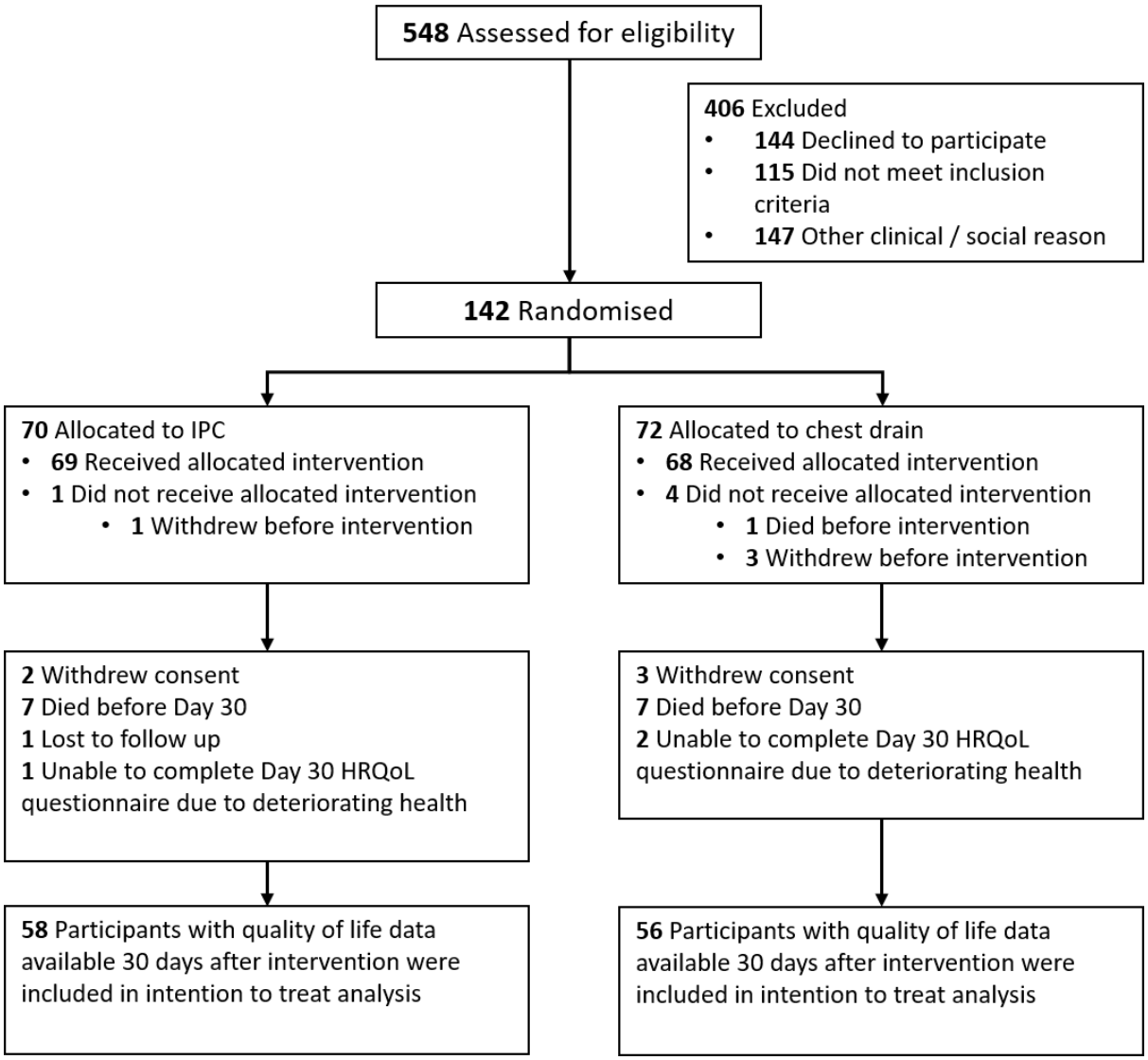


Figure 1: Consort diagram for OPTIMUM Study.

Abbreviations: HRQoL – health related quality of life; IPC – indwelling pleural catheter.

Baseline characteristics

Of the 142 randomised patients, two patients that withdrew following randomisation did not consent to baseline data collection. Baseline data for both groups are presented in Table 1.

236

237 Table 1: Summary of baseline characteristics

	IPC (n=70)	Chest Drain (n=70)
Age, mean (SD), yr	69.0 (12.5)	66.5 (12.7)
Female : Male	38 : 32	42 : 28
Tobacco smoking status (%)		
Current smoker	6 (8.6%)	5 (7.1%)
Former smoker	36 (51.4%)	45 (64.2%)
Never smoked	28 (40%)	19 (27.1%)
Unknown	-	1 (1.4%)
Side of intervention (%)		
Right	48 (68.6%)	39 (55.7%)
Left	22 (31.4%)	31 (44.3%)
Bilateral pleural effusion (%)	12 (17.1%)	13 (18.6%)
WHO performance status		
0	9 (12.8%)	5 (7.1%)
1	32 (45.8%)	32 (45.8%)
2	23 (32.9%)	26 (37.1%)
3	6 (8.6%)	7 (10%)
Malignancy		
Lung	22 (31.4%)	21 (30%)
Breast	18 (25.7%)	15 (21.4%)
Mesothelioma	9 (12.9%)	12 (17.1%)
Renal	5 (7.1%)	4 (5.7%)
Ovarian	5 (7.1%)	3 (4.3%)
Unknown Primary	4 (5.7%)	4 (5.7%)
Colorectal	2 (2.9%)	2 (2.9%)
Upper gastrointestinal	1 (1.4%)	2 (2.9%)
Uterine	1 (1.4%)	3 (4.3%)
Other	3 (4.3%)	4 (5.7%)
Duration of cancer diagnosis at the time of recruitment, mean (SD), months	26.1 (40.8)	15.6 (28.3)
Treatment at enrolment	n=29	n=27
Chemotherapy	13 (18.6%)	13 (18.6%)
Targeted (e.g. HER2, ALK, EGFR, multikinase)	9 (12.9%)	6 (8.6%)
Hormonal	4 (5.7%)	5 (7.1%)
Immunotherapy	3 (4.3%)	3 (4.3%)
Steroid therapy at baseline	9 (12.9%)	5 (7.1%)

Size of effusion on chest radiograph		
<25% hemithorax	7 (10%)	12 (17.1%)
25-50% hemithorax	25 (35.7%)	29 (41.4%)
>50% hemithorax	34 (48.6%)	25 (35.7%)
EORTC QLQ-C30 global health status at baseline, mean (SD)	n=70 37.3 (25.4)	n=69 37.8 (25.4)
100mm VAS breathlessness score at baseline, mean (SD)	n=68 60.8 (26.0)	n=67 50.3 (28.4)

Abbreviations: WHO – World Health Organization; HER2 - human epidermal growth factor receptor *2*, ALK - anaplastic lymphoma kinase; EGFR - epidermal growth factor receptor; EORTC QLQ-C30 - European Organisation for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30; VAS – Visual Analogue Scale.

Primary Outcome

Data were available in 58 and 56 patients in the IPC and chest drain groups, respectively. Global health status improved significantly at day 30 post-intervention (compared with the baseline) in both the IPC group (mean difference 13.11 [95% CI 5.6 to 21.1]; $p = 0.001$) and the chest drain group (mean difference 10.11 [95% CI 4.5 to 15.7]; $p = 0.001$). 57% (33 of 58) of patients in the IPC group and 54% (30 of 56) in the chest drain group experienced a greater than 8 point improvement in global health status. Mean global health status at day 30 (primary endpoint) was 52.0 (SD 24.1) in the IPC group and 50.9 (SD 24.1) in the chest drain group with an observed mean difference at 30 days of 2.06 ([95% CI -5.86 to 9.99]; p = 0.61) when adjusted for baseline global health status as a covariate.

Findings from the sensitivity analysis remained consistent with the primary analysis; at 30 days, a mean difference (IPC vs drain) in global health status of 2.18 ([95% CI -5.62 to 9.99]; $p = 0.59$) was observed.

Secondary Outcomes

Secondary outcome data are summarised in Table 2, Figures 2, and 3.

Quality of Life at 60 and 90 days

At 60 days after the intervention, global health status data were available in 46 patients in the IPC group and in 45 patients in the chest drain group. The mean change in global health status from baseline at day 60 was 15.6 (SD 26.4) in the IPC arm ($n = 46$), and 7.96 (SD 26.9) in the chest drain arm ($n = 45$). The ANCOVA, (adjusted for baseline global health status) indicated an observed mean difference of 4.82 ([95% CI -4.59 to 14.23]; $p = 0.31$).

At day 90 after the intervention, 43 patients completed follow up in the IPC arm versus 39 in the chest drain group. The mean change in global health status from baseline at day 90 was 13.4 (SD 30.6) in the IPC arm, and 14.93 (SD 25.1) in the chest drain arm. The ANCOVA (adjusted for baseline global health status) indicated an observed mean difference of -3.12 ([95% CI -13.76 to 7.51]; p = 0.56).

Pleurodesis Failure

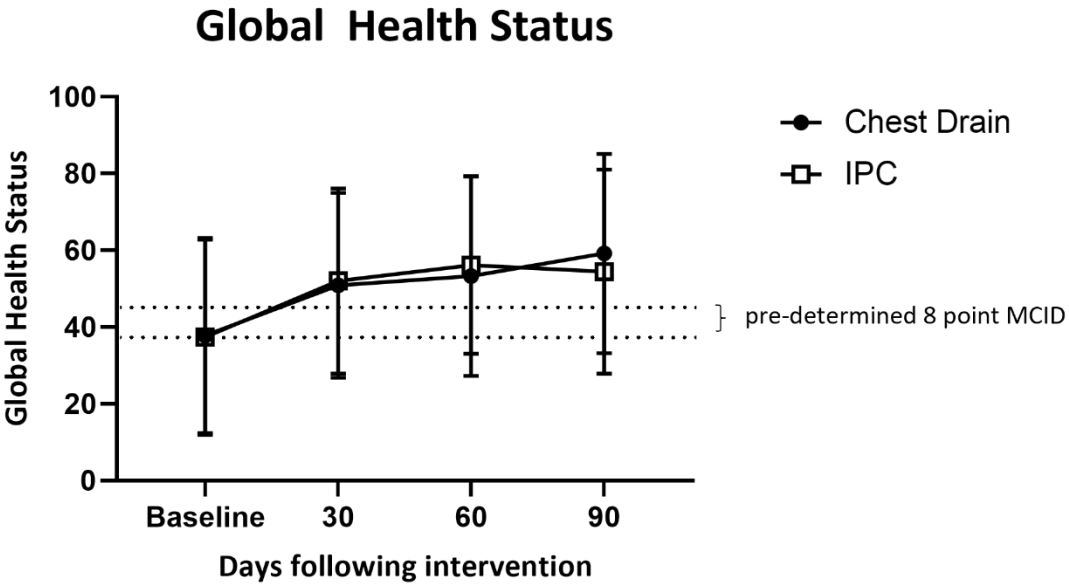
Figure 3 summarises outcomes related to talc pleurodesis and subsequent pleural intervention in both treatment arms.

Twenty-nine of 65 patients (44.6%) in the IPC arm received talc slurry vs 49 of 67 patients (73.1%) in the chest drain arm. The incidence of non-expandable lung (defined as <50% pleural apposition following drainage) was similar in both groups (IPC 15 (23.0%) vs chest drain 16 (23.9%)).

Thirteen participants in the IPC and talc instillation subgroup were eligible for IPC removal at Day 14, however 10 participants underwent IPC removal with the remaining three electing not to have the IPC removed. The rate of pleurodesis failure at 30 days in the IPC group (*defined as IPC remaining in situ, need for subsequent pleural intervention or chest x-ray opacification of >25% hemithorax*) was 64.3% (18 of 28), which includes the 3 participants that declined catheter removal at day 14. 4 IPCs were removed after day 30 due to pleurodesis: 1 IPC was removed after day 30 and 3 IPCs were removed after day 60. The pleurodesis failure rate at day 60 was 64.3% (18 of 28). At day 90, this was 57.1% (16 of 28).

Pleurodesis failure in the chest drain group (*defined as a need for subsequent pleural intervention or chest x-ray opacification of >25% hemithorax*) at 30 days was 18.4% (9 of 49). At day 60 this was 24.5% (12 of 49). At day 90 this was 26.5% (13 of 49).

A summary of patients that underwent an additional pleural intervention is provided in section 2.1 of Supplement 2.



IPC	70	58	46	43
Chest Drain	69	56	45	39

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289 Figure 2: Global health status scores measured using the EORTC QLQ C-30 over the 90-day follow-up
290 period. Points represent the mean, and bars represent standard deviation. Higher values indicate
291 better global health status. Table below graph denotes the number of patients with global health
292 status data at each time point. IPC – indwelling pleural catheter.

293

294 Table 2: Secondary outcome results

	Chest drain arm (*n* = 72)[a]	**IPC arm (*n* = 70)[a]**	**Treatment effect estimate (95% CI)**	***p*-value**
Change in global health status from baseline, mean (SD)	(*n* = 69 with ≥ 1 measurement)	(*n* = 70 with ≥1 measurement)	Absolute difference [b]	
Baseline	37.8 (25.4)	37.3 (25.4)		
Day 60	8.0 (26.9)	15.6 (26.4)	4.82 (-4.59 to 14.23)	0.31
Day 90	14.9 (25.1)	13.4 (30.6)	-3.12 (-13.76 to 7.51)	0.56
Change in VAS breathlessness score from baseline, mean (SD), mm	(*n* = 67 with ≥ 1 measurement)	(*n* = 68 with ≥1 measurement)	Absolute difference [c]	
Baseline	50.3 (28.4)	60.8 (26.0)		
Day 30	-19.9 (30.4)	-34.3 (28.4)	-6.8 (-15.97 to 2.41)	0.15
Day 60	-14.4 (32.3)	-30.3 (30.3)	-5.3 (-16.67 to 6.15)	0.37
Day 90	-17.3 (33.0)	-23.1 (41.4)	9.6 (-3.88 to 23.11)	0.17
Change in VAS chest pain score from baseline, mean (SD), mm	(*n* = 67 with ≥ 1 measurement)	(*n* = 68 with ≥1 measurement)	Absolute difference [c]	
Baseline	20.7 (27.1)	22.1 (27.1)		
Day 30	-1.9 (24.1)	-7.5 (24.7)	-2.84 (-9.69 to 4.02)	0.42
Day 60	-0.6 (22.0)	0.6 (30.0)	3.7 (-5.01 to 12.44)	0.41
Day 90	-4.27 (25.3)	2.8 (34.1)	8.7 (-2.79 to 20.17)	0.14
Pleurodesis failure, number (%)	(*n* = 49)	(*n* = 28)	Unadjusted odds ratio	
Day 30	9 (18.4%)	18 (64.3%)	8.0 (2.77 to 23.1)	<0.001
Day 60	12(24.5%)	18 (64.3%)	5.55 (2.02 to 15.25)	<0.001
Day 90	13 (26.5%)	16 (57.1%)	3.7 (1.38 to 9.8)	0.01

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296 VAS – visual analogue scale.

297 a: Unless otherwise stated.

298 b: ANCOVA adjusted for baseline global health status as a covariate.

299 c: Adjusted regression model for the stratification factors: (age [≤65years, >65years], WHO performance status [0,1,2 or 3],
300 underlying malignancy [mesothelioma, breast cancer, lung cancer or other]).

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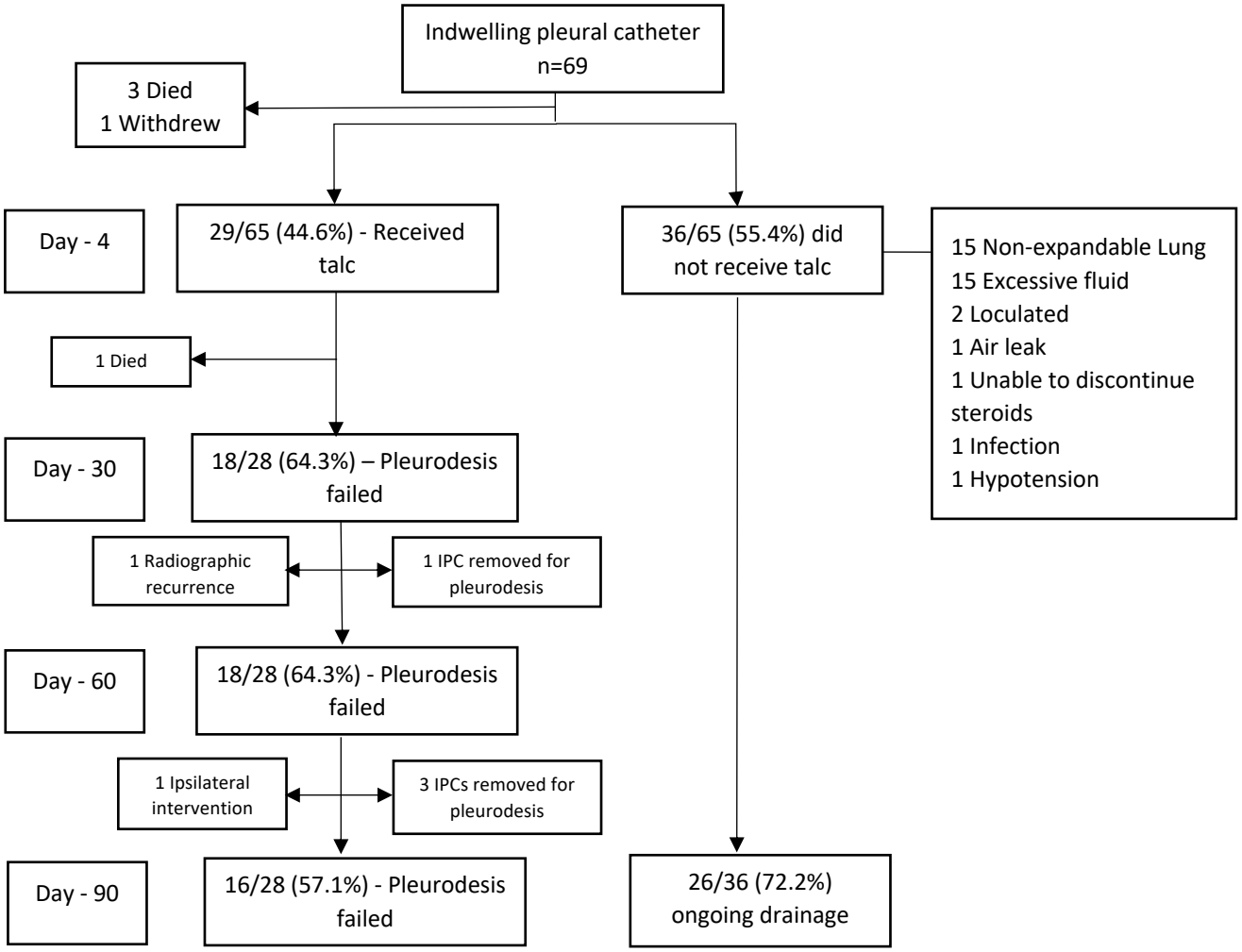
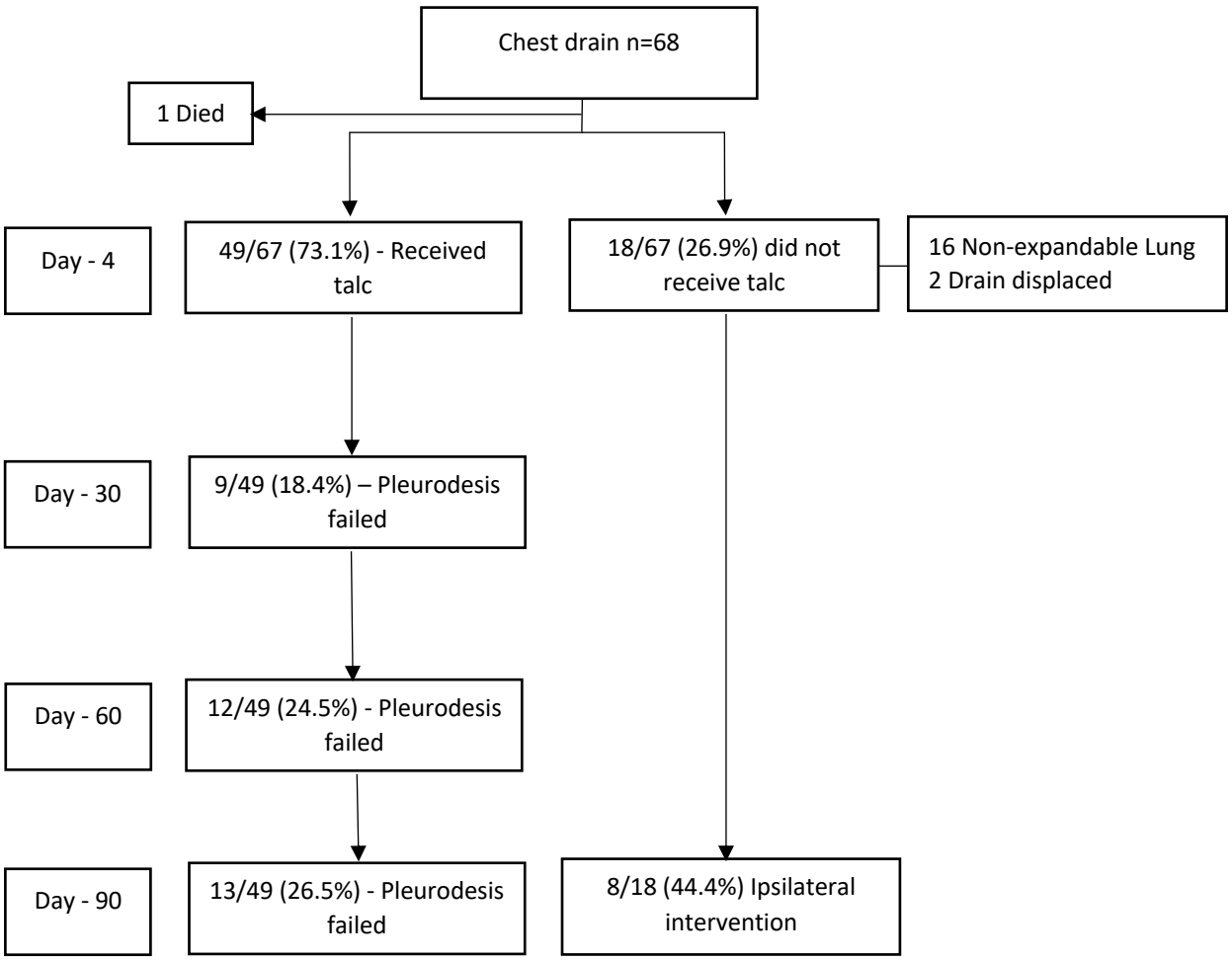


IPC + talc *–1 participant experienced re-accumulation of effusion (>25% hemithorax) after day 30, but did not undergo a subsequent intervention. 1 participant underwent subsequent ipsilateral pleural intervention after day 60. 4 IPCs were removed for delayed spontaneous pleurodesis: 1 IPC between day 30 and 60, 3 between day 60 and 90.*

IPC and no talc *– 10/36 (27.8%) participants had spontaneous pleurodesis and IPC removal: 1 before day 30, 5 between day 30 and day 60, 4 between day 60 and day 90. 5 participants underwent ipsilateral pleural intervention before day 90.*

Figure 3a: Pleurodesis failure in the IPC group. IPC – indwelling pleural catheter.



Chest drain + talc *– 13/49 (26.5%) patients were classified as pleurodesis failure at day 90: 8 had an ipsilateral intervention; 5 met pleurodesis failure criteria on the basis of chest x-ray opacification alone.*

Chest drain and no talc *– 8/18 (44.4%) underwent an ipsilateral pleural intervention before day 90.*

Figure 3b: Talc pleurodesis, additional pleural interventions and pleurodesis failure in the chest drain group.

Adverse Events

Adverse events are shown in Table 4, with more information in eTable S1 (Supplement 2). 83 events were recorded in the IPC group and 63 in the chest drain group occurring in 48 and 43 patients, respectively. There were more trial-related adverse events in the IPC group (26) vs the chest drain group (13).

Median per protocol hospitalization for chest drain patients was 4 days. There were 26 additional hospitalizations in the chest drain arm; none of these hospitalizations was related to the trial intervention. There were an additional 40 hospitalizations in the IPC arm; 7 of 40 were deemed intervention related. Two patients in the IPC arm were admitted primarily due to anxiety related to their indwelling catheter.

Thirty-six patients died (20 in the chest drain arm and 16 in the IPC arm). One patient died in the IPC arm due to pleural infection on a background of advanced malignancy. The odds ratio for death was 0.71 (95% CI, 0.33 to 1.52, p=0.39).

Table 4: Reported adverse events

	No. of events	
Adverse Event	Chest Drain (n=63)	IPC (n=83)
Intervention related serious adverse event	0	7
Hospital admission for drain related anxiety	-	2
Hospital admission for drain related pain	-	1
Hospital admission with pleural infection	-	1
Hospital admission with pleurodesis related pain	-	1
Pre-pleurodesis steroid withdrawal	-	1
Post insertion oxygen requirement	-	1
Intervention related adverse event	13	19
Pleurodesis related pain	1	1
Drain related pain	-	4
Hydropneumothorax with air leak	1	2
Pleurodesis related fever	1	-
Cutaneous infection	2	5
Pleural infection	1	1
Tube displacement	1	2
Drain blockage	5	2
Tract metastasis	-	1
Vasovagal syncope during insertion	1	-
Failed drain insertion	-	1
Events not related to intervention	50	57
Death	20	16
Admission for symptom control / cancer progression (non-intervention related)	9	10
Other (see eTable S1)	21	31

Post-hoc analysis

Data were examined on physical, social, emotional, cognitive and role functional domains. These results are summarised in Supplement 2 (Figure S4 and eTable S4).

Discussion

To the best of our knowledge, this is the first multicentre, open-label randomised controlled trial to investigate the impact of management of MPE on HRQoL as a primary outcome.

Within the limits of the study, our findings suggest that the outpatient IPC pathway was not superior to inpatient treatment with a chest drain and talc slurry in improving global health status, as measured by the EORTC QLQ C-30 questionnaire at 30 days post-intervention. However, both treatment approaches delivered sustained improvements in global health status at 60 and 90-days. These findings align closely with HRQoL outcomes observed in the TIME2 trial, where both approaches yielded similar EORTC QLQ C-30 outcomes in a smaller patient cohort[12]. Additionally, another interventional study assessing HRQoL as a secondary measure, did not identify any significant differences between the outpatient and inpatient treatment pathways over 1 year of follow up when utilising the EQ 5D-5L and the 100mm VAS tools[4].

IPCs are increasingly being used as a first line treatment in the management of symptomatic, recurrent malignant pleural effusion in some parts of the world, despite a lack of trial data to support its superiority over chest drain and talc pleurodesis in symptom control and hospital length of stay in the year after intervention[4]. A key goal of treatment is to improve health-related quality of life, and given our findings, we advocate that patients select a treatment pathway best suited for their overall health, psychological and social circumstances. However, the outpatient pathway is a multifaceted intervention, requiring a secure framework of community healthcare support. In regions where this may not be viable, we recommend opting for a chest drain and talc pleurodesis.

Our study also examined pleurodesis failure as a secondary outcome. This was significantly higher in the IPC arm than in the chest drain arm (69% vs 26.5% at 90 days, respectively). Several reasons may explain this finding. The definition of talc pleurodesis failure in the outpatient arm included patients in whom the IPC remained in situ despite successful pleurodesis; chosen because a key aim of offering pleurodesis via an IPC is to promote expeditious catheter removal. Three of 13 (23%) eligible patients chose not to have their IPCs removed following successful pleurodesis, highlighting the anxiety surrounding fluid recurrence. Patients in the IPC group had larger effusions, and more were receiving systemic steroid therapy at the time of trial recruitment; which may have had an effect.[13, 14]

The IPC-PLUS trial, which primarily examined pleurodesis outcomes via an IPC, reported a 43% pleurodesis success rate at 35 days post-talc insufflation,[2] which is slightly higher than the rate of pleurodesis success at Day 30 (35%) in this study. However, differences in drainage protocols (affecting the degree of pleural apposition) and patient selection may account for this disparity.

Of note, there were significantly more intervention related adverse events in the outpatient treatment arm, particularly hospitalization due to an intervention-related adverse event (7 vs 0). Given the lack of superiority of outpatient management for the primary outcome measure and similar outcomes, these findings may suggest that chest drain and talc pleurodesis may be the preferred treatment option in some patients.. Therefore, we advocate careful consideration and counselling of the potential risks before offering management with an IPC.

The main limitation is the data attrition for the primary outcome. Despite this, the findings still contribute valuable insights into HRQoL outcomes. Significant improvements in global health status were seen in both treatment arms with the observed difference well below clinically significant levels, and these findings are also supported by the sensitivity analysis. This study reflects the considerable practical challenges faced in conducting studies in this population, particularly when implementing complex interventions in a real-world context. Strategies to mitigate attrition in future studies in this area may include utility of a scoring tool for prognostication or delivery of the study follow-up within the patient's home setting.

The EORTC QLQ-C30 questionnaire used to assess overall HRQoL was selected due to its validation in the cancer population. However, the minimal important difference (MID) for the EORTC QLQ-C30 global health status scale varies in different cancer populations. The MID chosen for the primary outcome analysis was selected based on a combination of previously published data in the lung and breast cancer population. More importantly, this has not been specifically defined in the MPE population and to the best of our knowledge, there is no HRQoL questionnaire that is specifically designed and validated for patients with MPE. A bespoke questionnaire focused on a combination of physical, emotional and social functions in patients within the last year of life may be useful in understanding outcomes in these other domains. Only patients with a performance status of less than 3 and an expected prognosis of 3 months were included, as assessed by the treating clinician. This was to ensure patients committed to the outpatient treatment pathway would be ambulant and well enough to undertake the requirements of the study. Therefore these results may not be applicable to a key group of patients with poorer performance status and shorter life expectancy.

The outpatient pathway is resource intensive, especially concerning community nursing assistance, expenses linked to drainage bottles, and the hospital resources required for administering outpatient

talc treatment. Despite the promotion of ambulatory management approaches by policymakers, these demands might not be achievable in every setting.

To summarise, this study suggests that treatment using an IPC and managing as outpatient is not superior to inpatient chest drain and pleurodesis at improving HRQoL. However, the IPC pathway is associated with an increased rate of adverse events. An informed treatment choice should be made based on patient preferences, acceptability of risk, social circumstances, values, affordability and treatment accessibility.

Contributors

Sivakumar, Douiri and Ahmed had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Ahmed, Sivakumar, Rao, Douiri

Acquisition, analysis, or interpretation of data: All authors

Drafting of the manuscript: Sivakumar, Ahmed

Critical revision of the manuscript: All authors

Statistical analysis: Douiri, Sun

Obtained funding: Ahmed

Administrative, technical, or material support: Wallace, Noorzad, West, Simpson, Sivakumar, Ahmed

Declaration of interests

Dr. Ahmed reported receiving grants from GE outside the submitted work.

Dr. Sivakumar reported receiving grants from Rocket Medical outside the submitted work.

Dr. Fitzgerald reports grants from European Respiratory Society outside the submitted work.

Professor. Maskell reports grants and personal fees from Beckton Dickinson and Company outside of the submitted work.

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Role of the Funder/Sponsor

Neither the funder nor the sponsor had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

References

1. Clive AO, Kahan BC, Hooper CE, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax* 2014: 69(12): 1098-1104.
2. Bhatnagar R, Keenan EK, Morley AJ, et al. Outpatient talc administration by indwelling pleural catheter for malignant effusion. *New England Journal of Medicine* 2018: 378(14): 1313-1322.
3. Wahidi MM, Reddy C, Yarmus L, et al. Randomized trial of pleural fluid drainage frequency in patients with malignant pleural effusions. The ASAP trial. *American journal of respiratory and critical care medicine* 2017: 195(8): 1050-1057.
4. Thomas R, Fysh ET, Smith NA, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. *Jama* 2017: 318(19): 1903-1912.
5. Sivakumar P, Saigal A, Ahmed L. Quality of life after interventions for malignant pleural effusions: a systematic review. *BMJ Supportive & Palliative Care* 2020: 10(1): 45-54.
6. Sivakumar P, Douiri A, West A, et al. OPTIMUM: a protocol for a multicentre randomised controlled trial comparing Out Patient Talc slurry via Indwelling pleural catheter for Malignant pleural effusion vs Usual inpatient Management. *BMJ open* 2016: 6(10).
7. Roberts ME, Neville E, Berrisford RG, et al. Management of a malignant pleural effusion: British Thoracic Society pleural disease guideline 2010. *Thorax* 2010: 65(Suppl 2): ii32-ii40.
8. Scott NW, Fayers P, Aaronson NK, et al. EORTC QLQ-C30 reference values manual. 2008.
9. Fayers P, Aaronson NK, Bjordal K, et al. EORTC QLQ–C30 scoring manual. European Organisation for Research and Treatment of Cancer, 1995.
10. Azur MJ, Stuart EA, Frangakis C, et al. Multiple imputation by chained equations: what is it and how does it work? *International journal of methods in psychiatric research* 2011: 20(1): 40-49.
11. Buuren Sv, Groothuis-Oudshoorn K. mice: Multivariate imputation by chained equations in R. *Journal of statistical software* 2010: 1-68.
12. Davies HE, Mishra EK, Kahan BC, 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): 2383-2389.
13. Xie C, Teixeira LR, McGovern JP, et al. Systemic corticosteroids decrease the effectiveness of talc pleurodesis. *American journal of respiratory and critical care medicine* 1998: 157(5 Pt 1): 1441-1444.
14. Hassan M, Gadallah M, Mercer RM, et al. Predictors of outcome of pleurodesis in patients with malignant pleural effusion: a systematic review and meta-analysis. *Expert review of respiratory medicine* 2020: 14(6): 645-654.