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1   # The impact of outpatient vs inpatient management on health-related

2   # quality of life outcomes for patients with malignant pleural effusion –

3   # 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.

122   Methods

123   *Trial Design*

124   The Out Patient Talc Slurry via Indwelling Pleural Catheter for Malignant Pleural Effusion Vs Usual

125   Inpatient Management (OPTIMUM) trial is a randomised, two-arm, open-label superiority trial

126   conducted at 11 hospitals in the United Kingdom and one hospital in Australia. UK ethics approval

127   was obtained from the National Research Ethics Service (NRES) Committee South East Coast,

128   Brighton and Sussex (15/LO/1018). For Australia, approval was obtained from the Sir Charles

129   Gairdner Group Human Research Ethics Committee. The trial protocol has been published[6]

130   (Supplement 1).

131   *Participants*

132   All participants were adults diagnosed with MPE made either by histocytological confirmation or

133   clinical and radiological features of metastatic pleural disease in patients with histologically proven

134   primary cancers. Participants were required to have a WHO performance status of two or less,

135   unless a performance status of three was likely to improve with pleural drainage. Participants also

136   needed an expected survival of greater than three months. The exclusion criteria were age less than

137   18 years old; pregnant or lactating; known allergy to talc or lidocaine; lack of symptomatic relief

138   from effusion drainage; district nurse/carers/hospital team unable to carry out at least twice weekly

139   IPC drainage; underlying lymphoma or small cell carcinoma except if chemotherapy had failed or the

140   patient was to be referred for palliative management; non-malignant effusions; loculated pleural

141   effusion; and patients unable to provide written informed consent to trial participation. Participants

142   were screened from both the outpatient and inpatient setting.

143   *Randomization*

144   Participants were randomised 1:1 to either IPC insertion or chest drain and talc slurry pleurodesis.

145   Permuted block randomisation (block sizes 4, 6, 8) was performed with allocation concealment

146   maintained using a web-based randomisation service (www.sealedenvelope.com). Treatment

147   allocation was unblinded and stratified to the following factors: age (<65 years, $\geq$65 years),

148   malignancy subtype (lung, mesothelioma, breast, other) and WHO performance status (0, 1, 2, 3).

149   Patient blinding was not practical due to inherent differences between the interventions.

150

151   *Procedures*

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

153   interventions.

154 Participants randomised to the IPC group underwent catheter insertion as a day case under local

155 anaesthesia using a percutaneous Seldinger technique. Following insertion, an attempt was made to

156 evacuate the fluid completely, using pleural manometry where available, to enable safe large-

157 volume drainage and reduce the risk of re-expansion pulmonary oedema. Patients then returned

158 after three days for review and a further attempt at maximal pleural fluid drainage. If the fluid

159 removed at this visit averaged less than 150mls/day since IPC insertion and non-expandable lung

160 was ruled out by ultrasound or X-ray, talc pleurodesis was attempted through the IPC. The protocol

161 was amended in October 2016 to remove the <150mls/day drainage criteria as feedback from

162 recruiting centres suggested incomplete drainage at insertion made fluid estimation at the day 4 visit

163 difficult. Four grams of sterile talc was then administered as a slurry (section 1.1.1 in Supplement 2)

164 and participants observed for 1 hour following instillation. Patients or district nurses were advised to

165 perform daily IPC drainages as an 'aggressive' drainage strategy using 1 litre bottles and return at

166 day 7 for review, chest X-ray and repeat drainage. If satisfactory pleural apposition with absence of

167 pleural sliding was seen on ultrasound in 5 of 6 areas (Figure s3 in Supplement 2), repeated drainage

168 was halted. Participants returned on day 14 for review and the IPC removed if pleural apposition was

169 maintained with evidence of minimal fluid on ultrasound.

170 In cases where talc instillation was either not attempted or in participants that did not meet the

171 criteria for IPC removal at day 14, regular IPC drainage was continued throughout the study follow

172 up period. The frequency of drainage was at the discretion of the treating physician. For these

173 participants, the recommended approach was early assessment in the clinic if they experienced

174 three consecutive drainages of less than 50mls of fluid. If either a chest x-ray or ultrasound showed

175 no significant residual pleural collection, then the IPC could be removed.

176 Participants randomised to chest drain and talc pleurodesis underwent management as per the 2010

177 British Thoracic Society (BTS) pleural disease guidelines[7]. A 12F-14F chest drain was inserted using

178 ultrasound guidance under local anaesthesia, and the patient was admitted to hospital. After 24hrs,

179 if the chest X-ray ruled out an non-expandable lung, 4 grams of talc slurry was instilled. The drain

180 was then removed when the pleural fluid output dropped below 250mls/day. Patients with non-

181 expandable lung or any other contraindication to talc slurry pleurodesis (such as an air leak) could be

182 managed using an alternative strategy and continued their follow up in the study.

183 *Follow-up*
184 All participants underwent follow up until 90 days after intervention or death, whichever occurred

185 first. Trial visits were conducted at the outpatient clinic on day 4 for the IPC group and 7, 14, 30, 60

186 and 90 days after the intervention for both groups. If fluid recurrence or complications developed,

187   the trial clinicians were permitted to perform further tests and procedures (e.g. IPC insertion or

188   referral for thoracic surgery) as part of usual clinical care.

189   *Outcomes*

190   Primary Outcome

191   The primary outcome was global health status, at 30 days post-intervention measured with the

192   European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Cancer

193   30 (EORTC QLQ C-30). This is a validated, cancer specific, multidimensional instrument that asks

194   participants to report on aspects of their health-related quality of life over the previous week. It is

195   suitable for all cancer diagnoses[8] and can be repeated at frequent intervals to monitor quality of

196   life over time[9].

197   Secondary Outcomes

198   Secondary outcomes included global health status at day 60 and day 90 post-intervention, adverse

199   event rates, breathlessness, chest pain scores and pleurodesis failure rate. Pleurodesis failure was

200   defined as chest X-ray opacification greater than 25% on the side of intervention or the need for

201   subsequent pleural intervention on the same side as pleurodesis at 30, 60 and 90 days post-

202   intervention. Breathlessness and chest pain scores at 30, 60 and 90 days post-intervention were

203   measured using the 0-100mm visual analogue scale.

204   *Statistical analysis*

205   Using an analysis of covariance model (ANCOVA), adjusting for baseline global health status, a

206   sample size of 142 (71 vs 71) would detect a clinically significant difference of 8 points in global

207   health status with 80% power and a 5% significance level. This assumes a common standard

208   deviation of 23.6 in Stage III-IV cancer[8]. The covariate has an R-squared of 0.49. An interim analysis

209   was planned once 50% of patients were enrolled to determine if the recruitment target needed

210   amendment.

211   At this interim analysis, a blinded assessment of data demonstrated a 14% loss to follow-up at 30

212   days. The trial steering committee agreed that given funding, recruitment rates and the nature of

213   the patient population, increasing the sample size would not be feasible and agreed to continue

214   recruitment until December 2019 to achieve the original trial objective.

215   Data were analysed on an intention-to-treat basis in all patients in whom outcome data were

216   available. The primary efficacy analysis was based on ANCOVA. Regression analyses were adopted to

217   compare estimates for secondary efficacy analyses.

218   Data attrition for the complete case analysis prompted a post-hoc sensitivity analysis. Multiple

219   imputation by chained equations was used to impute the missing data[10]. Using mice (Multivariate

220   Imputation by Chained Equations) R package[11], 300 simulated datasets were generated, and an

221   ANCOVA analysis was performed on all of the imputed datasets with the results pooled. All analyses

222   were conducted using R version 4.0. The trial statistical analysis plan is outlined in Supplement 3.

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

224   Results

225   After screening a total of 548 patients for eligibility, 142 participants were recruited between July

226   2015 and November 2019. Four patients withdrew, and one died before undergoing the randomised

227   intervention. They were excluded from the analyses (Figure 1).
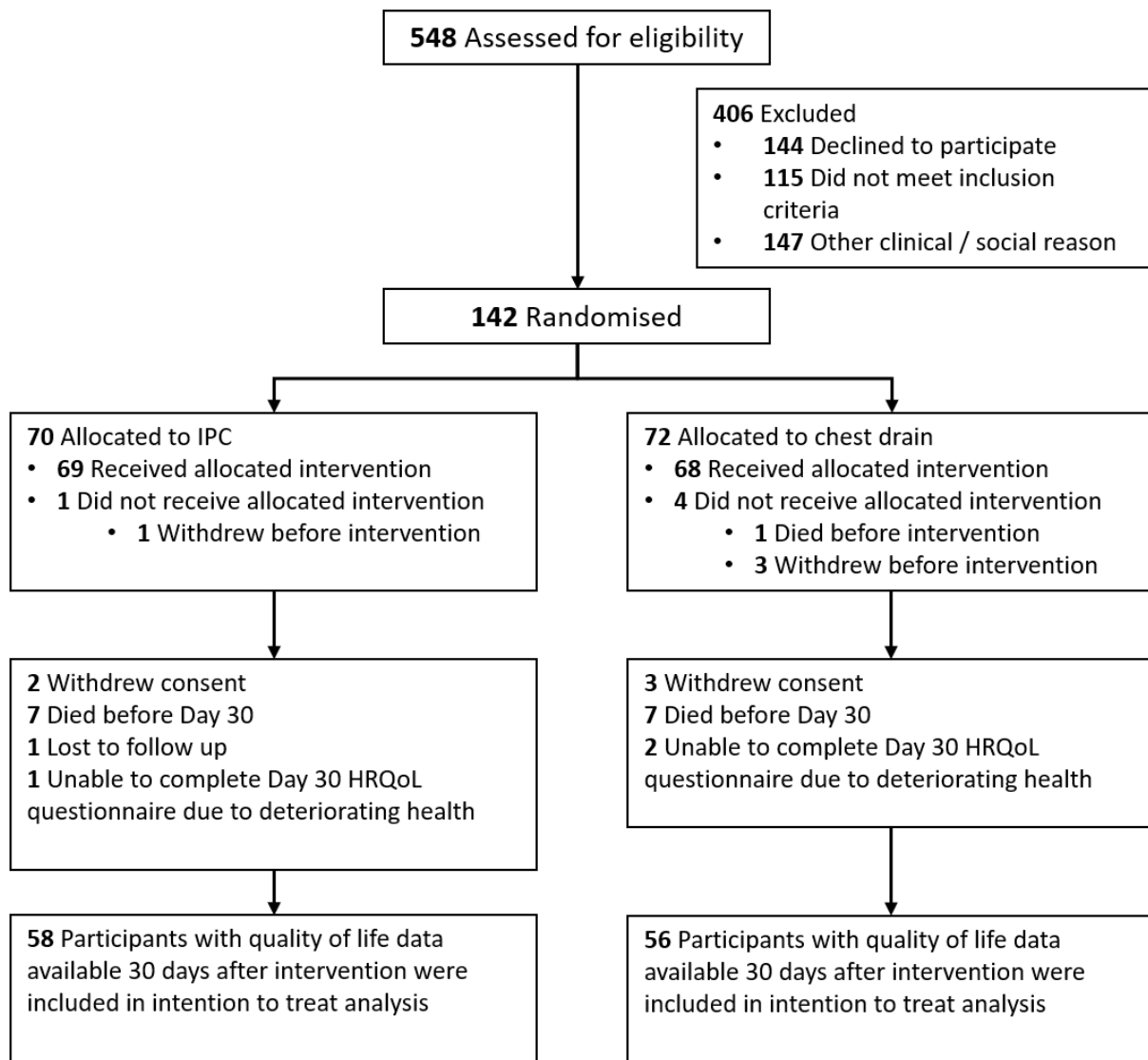
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229   Figure 1: Consort diagram for OPTIMUM Study.

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

231

232   *Baseline characteristics*

233   Of the 142 randomised patients, two patients that withdrew following randomisation did not

234   consent to baseline data collection. Baseline data for both groups are presented in Table 1.

235

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)

238

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

242

243 *Primary Outcome*

244 Data were available in 58 and 56 patients in the IPC and chest drain groups, respectively. Global

245 health status improved significantly at day 30 post-intervention (compared with the baseline) in

246 both the IPC group (mean difference 13.11 [95% CI 5.6 to 21.1]; *p* = 0.001) and the chest drain group

247 (mean difference 10.11 [95% CI 4.5 to 15.7]; *p* = 0.001). 57% (33 of 58) of patients in the IPC group

248 and 54% (30 of 56) in the chest drain group experienced a greater than 8 point improvement in

249 global health status. Mean global health status at day 30 (primary endpoint) was 52.0 (SD 24.1) in

250 the IPC group and 50.9 (SD 24.1) in the chest drain group with an observed mean difference at 30

251 days of 2.06 ([95% CI -5.86 to 9.99]; p = 0.61) when adjusted for baseline global health status as a

252 covariate.

253 Findings from the sensitivity analysis remained consistent with the primary analysis; at 30 days, a

254 mean difference (IPC vs drain) in global health status of 2.18 ([95% CI -5.62 to 9.99]; *p* = 0.59) was

255 observed.

256 *Secondary Outcomes*

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

258 Quality of Life at 60 and 90 days

259 At 60 days after the intervention, global health status data were available in 46 patients in the IPC

260 group and in 45 patients in the chest drain group. The mean change in global health status from

261 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

262 arm (*n* = 45). The ANCOVA, (adjusted for baseline global health status) indicated an observed mean

263 difference of 4.82 ([95% CI -4.59 to 14.23]; *p* = 0.31).

264 At day 90 after the intervention, 43 patients completed follow up in the IPC arm versus 39 in the

265 chest drain group. The mean change in global health status from baseline at day 90 was 13.4 (SD

266 30.6) in the IPC arm, and 14.93 (SD 25.1) in the chest drain arm. The ANCOVA (adjusted for baseline

267 global health status) indicated an observed mean difference of -3.12 ([95% CI -13.76 to 7.51]; *p* =

268 0.56).

269 *Pleurodesis Failure*

270 Figure 3 summarises outcomes related to talc pleurodesis and subsequent pleural intervention in

271 both treatment arms.

272 Twenty-nine of 65 patients (44.6%) in the IPC arm received talc slurry vs 49 of 67 patients (73.1%) in

273 the chest drain arm. The incidence of non-expandable lung (defined as <50% pleural apposition

274 following drainage) was similar in both groups (IPC 15 (23.0%) vs chest drain 16 (23.9%)).

275 Thirteen participants in the IPC and talc instillation subgroup were eligible for IPC removal at Day 14,

276 however 10 participants underwent IPC removal with the remaining three electing not to have the

277 IPC removed. The rate of pleurodesis failure at 30 days in the IPC group (*defined as IPC remaining in*

278 *situ, need for subsequent pleural intervention or chest x-ray opacification of >25% hemithorax*) was

279 64.3% (18 of 28), which includes the 3 participants that declined catheter removal at day 14. 4 IPCs

280 were removed after day 30 due to pleurodesis: 1 IPC was removed after day 30 and 3 IPCs were

281 removed after day 60. The pleurodesis failure rate at day 60 was 64.3% (18 of 28). At day 90, this

282 was 57.1% (16 of 28).

283 Pleurodesis failure in the chest drain group (*defined as a need for subsequent pleural intervention or*

284 *chest x-ray opacification of >25% hemithorax*) at 30 days was 18.4% (9 of 49). At day 60 this was

285 24.5% (12 of 49). At day 90 this was 26.5% (13 of 49).

286 A summary of patients that underwent an additional pleural intervention is provided in section 2.1

287 of Supplement 2.

Global Health Status
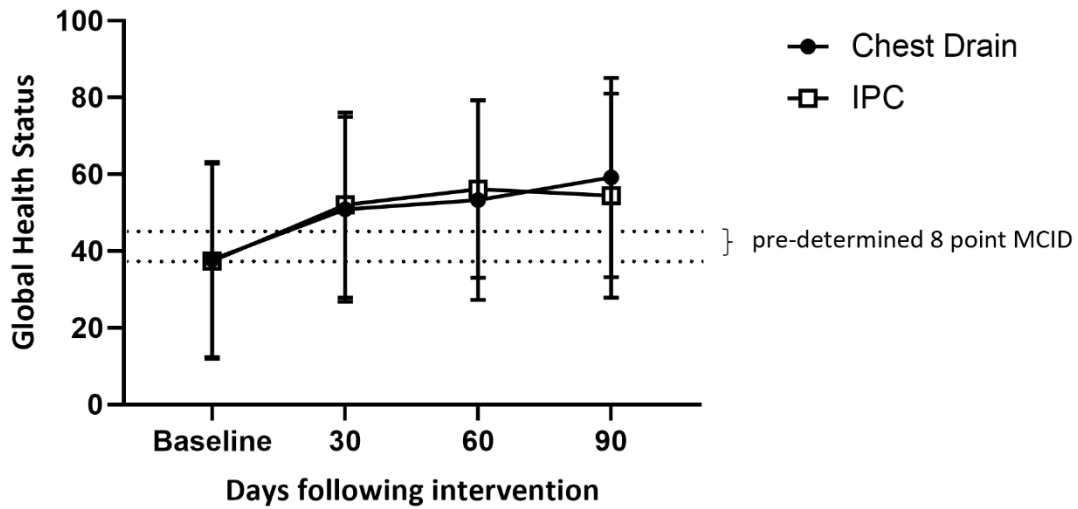
IPC	70	58	46	43
Chest Drain	69	56	45	39

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

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.

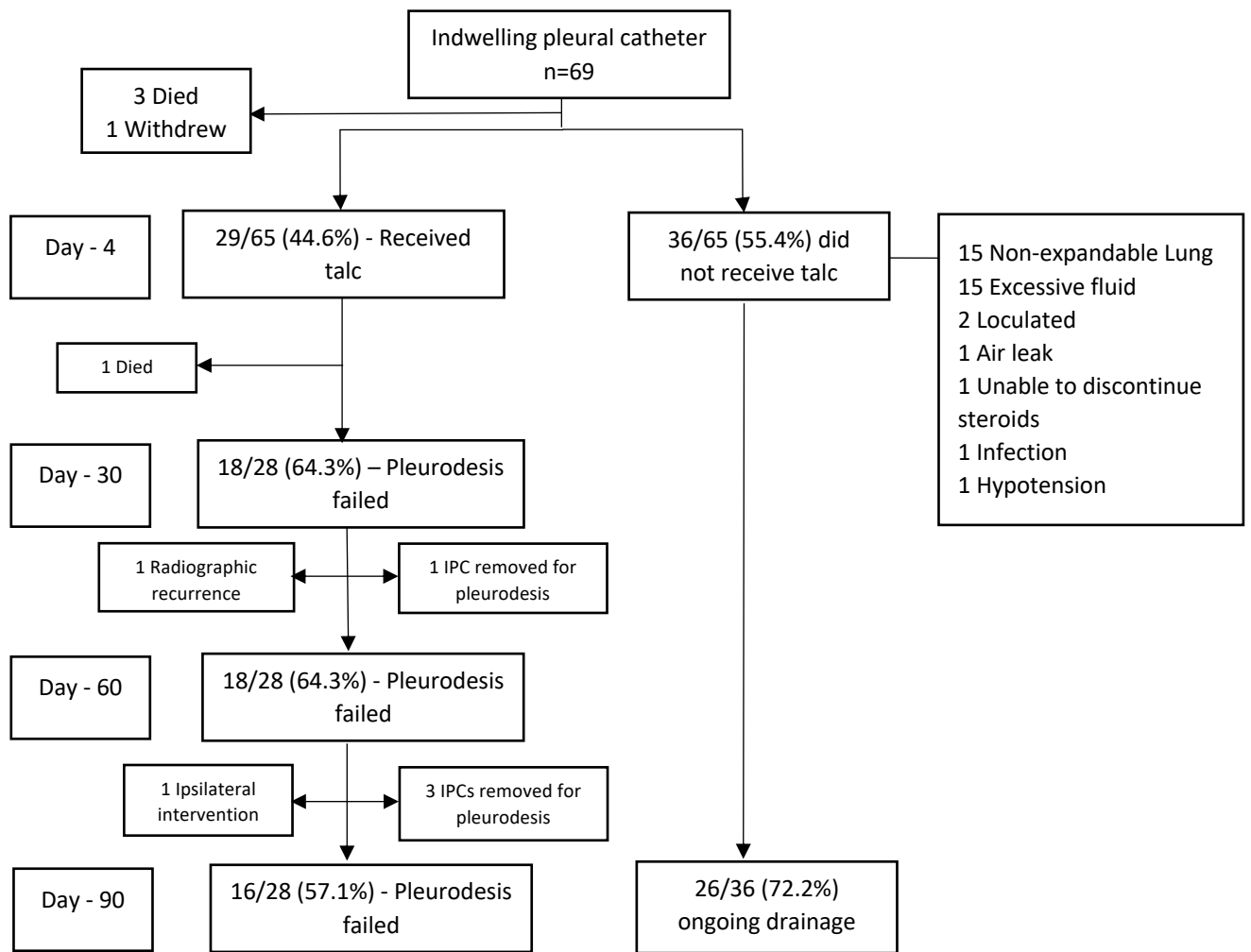297   a: Unless otherwise stated.

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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                              │  Indwelling pleural catheter   │
                              │            n=69                │
                              └────────────────────────────────┘
┌──────────────┐
│  3 Died      │◄─────────────
│  1 Withdrew  │
└──────────────┘
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| Day - 4 | 29/65 (44.6%) - Received talc | | 36/65 (55.4%) did not receive talc | 15 Non-expandable Lung
15 Excessive fluid
2 Loculated
1 Air leak
1 Unable to discontinue steroids
1 Infection
1 Hypotension |

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┌──────────┐
│  1 Died  │◄──────
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| Day - 30 | 18/28 (64.3%) – Pleurodesis failed |

| 1 Radiographic recurrence | ◄──► | 1 IPC removed for pleurodesis |

| Day - 60 | 18/28 (64.3%) - Pleurodesis failed |

| 1 Ipsilateral intervention | ◄──► | 3 IPCs removed for pleurodesis |

| Day - 90 | 16/28 (57.1%) - Pleurodesis failed | | 26/36 (72.2%) ongoing drainage |

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.*

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

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                          ┌─────────────────────────┐
                          │      Chest drain n=68    │
                          └─────────────────────────┘
        ┌─────────┐                    │
        │ 1 Died  │◄───────────────────┤
        └─────────┘            ┌───────┴────────┐
                               ▼                ▼
┌──────────┐  ┌──────────────────────┐  ┌──────────────────────┐  ┌──────────────────────┐
│ Day - 4  │  │ 49/67 (73.1%) -       │  │ 18/67 (26.9%) did not│  │ 16 Non-expandable Lung│
│          │  │ Received talc         │  │ receive talc         │  │ 2 Drain displaced     │
└──────────┘  └──────────────────────┘  └──────────────────────┘  └──────────────────────┘
                          │                         │
                          ▼                         │
┌──────────┐  ┌──────────────────────┐              │
│ Day - 30 │  │ 9/49 (18.4%) –        │              │
│          │  │ Pleurodesis failed    │              │
└──────────┘  └──────────────────────┘              │
                          │                         │
                          ▼                         │
┌──────────┐  ┌──────────────────────┐              │
│ Day - 60 │  │ 12/49 (24.5%) -       │              │
│          │  │ Pleurodesis failed    │              │
└──────────┘  └──────────────────────┘              │
                          │                         ▼
┌──────────┐  ┌──────────────────────┐  ┌──────────────────────┐
│ Day - 90 │  │ 13/49 (26.5%) -       │  │ 8/18 (44.4%) Ipsilateral│
│          │  │ Pleurodesis failed    │  │ intervention          │
└──────────┘  └──────────────────────┘  └──────────────────────┘
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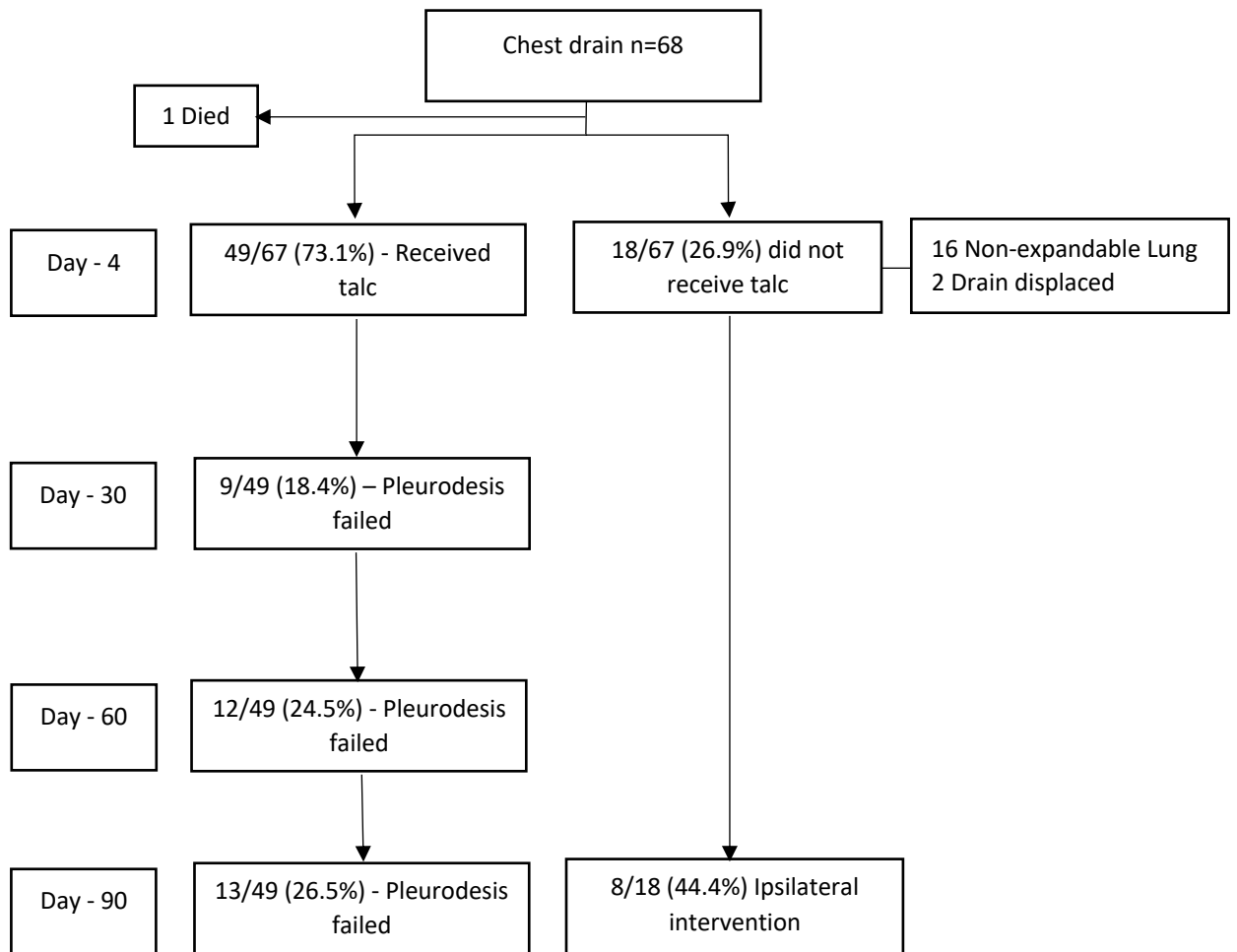
> *Chest drain + talc* – *13/49 (26.5%) patients were classified as pleurodesis failure at day 90: 8 had an ipsilateral intervention; 5 met pleurodesis failure criteria on the basis of chest x-ray opacification alone.*
>
> *Chest drain and no talc* – *8/18 (44.4%) underwent an ipsilateral pleural intervention before day 90.*

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

359

360 *Adverse Events*

361 Adverse events are shown in Table 4, with more information in eTable S1 (Supplement 2). 83 events

362 were recorded in the IPC group and 63 in the chest drain group occurring in 48 and 43 patients,

363 respectively. There were more trial-related adverse events in the IPC group (26) vs the chest drain

364 group (13).

365 Median per protocol hospitalization for chest drain patients was 4 days. There were 26 additional

366 hospitalizations in the chest drain arm; none of these hospitalizations was related to the trial

367 intervention. There were an additional 40 hospitalizations in the IPC arm; 7 of 40 were deemed

368 intervention related. Two patients in the IPC arm were admitted primarily due to anxiety related to

369 their indwelling catheter.

370 Thirty-six patients died (20 in the chest drain arm and 16 in the IPC arm). One patient died in the IPC

371 arm due to pleural infection on a background of advanced malignancy. The odds ratio for death was

372 0.71 (95% CI, 0.33 to 1.52, p=0.39).

373 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

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375

376 *Post-hoc analysis*

377 Data were examined on physical, social, emotional, cognitive and role functional domains. These

378 results are summarised in Supplement 2 (Figure S4 and eTable S4).

379

380 Discussion
381

382 To the best of our knowledge, this is the first multicentre, open-label randomised controlled trial to

383 investigate the impact of management of MPE on HRQoL as a primary outcome.

384 Within the limits of the study, our findings suggest that the outpatient IPC pathway was not superior

385 to inpatient treatment with a chest drain and talc slurry in improving global health status, as

386 measured by the EORTC QLQ C-30 questionnaire at 30 days post-intervention. However, both

387 treatment approaches delivered sustained improvements in global health status at 60 and 90-days.

388 These findings align closely with HRQoL outcomes observed in the TIME2 trial, where both

389 approaches yielded similar EORTC QLQ C-30 outcomes in a smaller patient cohort[12]. Additionally,

390 another interventional study assessing HRQoL as a secondary measure, did not identify any

391 significant differences between the outpatient and inpatient treatment pathways over 1 year of

392 follow up when utilising the EQ 5D-5L and the 100mm VAS tools[4].

393 IPCs are increasingly being used as a first line treatment in the management of symptomatic, recurrent

394 malignant pleural effusion in some parts of the world, despite a lack of trial data to support its

395 superiority over chest drain and talc pleurodesis in symptom control and hospital length of stay in the

396 year after intervention[4]. A key goal of treatment is to improve health-related quality of life, and

397 given our findings, we advocate that patients select a treatment pathway best suited for their overall

398 health, psychological and social circumstances. However, the outpatient pathway is a multifaceted

399 intervention, requiring a secure framework of community healthcare support. In regions where this

400 may not be viable, we recommend opting for a chest drain and talc pleurodesis.

401 Our study also examined pleurodesis failure as a secondary outcome. This was significantly higher in

402 the IPC arm than in the chest drain arm (69% vs 26.5% at 90 days, respectively). Several reasons may

403 explain this finding. The definition of talc pleurodesis failure in the outpatient arm included patients

404 in whom the IPC remained in situ despite successful pleurodesis; chosen because a key aim of offering

405 pleurodesis via an IPC is to promote expeditious catheter removal. Three of 13 (23%) eligible patients

406 chose not to have their IPCs removed following successful pleurodesis, highlighting the anxiety

407 surrounding fluid recurrence. Patients in the IPC group had larger effusions, and more were receiving

408 systemic steroid therapy at the time of trial recruitment; which may have had an effect.[13, 14]

409   The IPC-PLUS trial, which primarily examined pleurodesis outcomes via an IPC, reported a 43%

410   pleurodesis success rate at 35 days post-talc insufflation,[2] which is slightly higher than the rate of

411   pleurodesis success at Day 30 (35%) in this study. However, differences in drainage protocols

412   (affecting the degree of pleural apposition) and patient selection may account for this disparity.

413   Of note, there were significantly more intervention related adverse events in the outpatient treatment

414   arm, particularly hospitalization due to an intervention-related adverse event (7 vs 0). Given the lack

415   of superiority of outpatient management for the primary outcome measure and similar outcomes,

416   these findings may suggest that chest drain and talc pleurodesis may be the preferred treatment

417   option in some patients.. Therefore, we advocate careful consideration and counselling of the

418   potential risks before offering management with an IPC.

419   The main limitation is the data attrition for the primary outcome. Despite this, the findings still

420   contribute valuable insights into HRQoL outcomes. Significant improvements in global health status

421   were seen in both treatment arms with the observed difference well below clinically significant levels,

422   and these findings are also supported by the sensitivity analysis. This study reflects the considerable

423   practical challenges faced in conducting studies in this population, particularly when implementing

424   complex interventions in a real-world context. Strategies to mitigate attrition in future studies in this

425   area may include utility of a scoring tool for prognostication or delivery of the study follow-up within

426   the patient's home setting.

427   The EORTC QLQ-C30 questionnaire used to assess overall HRQoL was selected due to its validation in

428   the cancer population. However, the minimal important difference (MID) for the EORTC QLQ-C30

429   global health status scale varies in different cancer populations. The MID chosen for the primary

430   outcome analysis was selected based on a combination of previously published data in the lung and

431   breast cancer population. More importantly, this has not been specifically defined in the MPE

432   population and to the best of our knowledge, there is no HRQoL questionnaire that is specifically

433   designed and validated for patients with MPE. A bespoke questionnaire focused on a combination of

434   physical, emotional and social functions in patients within the last year of life may be useful in

435   understanding outcomes in these other domains. Only patients with a performance status of less than

436   3 and an expected prognosis of 3 months were included, as assessed by the treating clinician. This was

437   to ensure patients committed to the outpatient treatment pathway would be ambulant and well

438   enough to undertake the requirements of the study. Therefore these results may not be applicable to

439   a key group of patients with poorer performance status and shorter life expectancy.

440   The outpatient pathway is resource intensive, especially concerning community nursing assistance,

441   expenses linked to drainage bottles, and the hospital resources required for administering outpatient

442 talc treatment. Despite the promotion of ambulatory management approaches by policymakers, these

443 demands might not be achievable in every setting.

444 To summarise, this study suggests that treatment using an IPC and managing as outpatient is not

445 superior to inpatient chest drain and pleurodesis at improving HRQoL. However, the IPC pathway is

446 associated with an increased rate of adverse events. An informed treatment choice should be made

447 based on patient preferences, acceptability of risk, social circumstances, values, affordability and

448 treatment accessibility.

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450

451 *Contributors*

452 Sivakumar, Douiri and Ahmed had full access to all of the data in the study and take responsibility for

453 the integrity of the data and the accuracy of the data analysis.

454 Concept and design: Ahmed, Sivakumar, Rao, Douiri

455 Acquisition, analysis, or interpretation of data: All authors

456 Drafting of the manuscript: Sivakumar, Ahmed

457 Critical revision of the manuscript: All authors

458 Statistical analysis: Douiri, Sun

459 Obtained funding: Ahmed

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

461

462 *Declaration of interests*

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

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

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

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

468 Professor. Lee reports non-financial support from Rocket Med Plc, grants from Rocket Med PLC,
469 outside the submitted work.

470 No other disclosures were reported.

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