Word Count (text): 3854
Word Count (abstract): 306

# Comparing Cost of Indwelling Pleural Catheter vs. Talc Pleurodesis for Malignant Pleural Effusion

Erika D. Penz SM MD MSc FRCPC[1], Eleanor K. Mishra BM BCh MA (Cantab) MRCP DPhil[2], Helen E. Davies MD MRCP[3], Braden J. Manns MD MSc FRCPC[4], Robert F. Miller MB BS FRCP[5], Najib M. Rahman BM BCh MA (oxon) MRCP MSc DPhil[2]

[1]Department of Medicine, University of Saskatchewan, Saskatoon, Canada

[2]Oxford Respiratory Trials Unit, University of Oxford, Oxford, United Kingdom

[3]University Hospital of Wales, Cardiff, Wales

[4]Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Canada

[5]Research Department of Infection and Population Health, University College London, London

**Corresponding Author:** Dr. Erika Penz. Address: Rm 565 Ellis Hall, Royal University Hospital, 103 Hospital Drive, Saskatoon, Saskatchewan, S7N 0W8, edp131@usask.ca; telephone: 306 844-1009; fax: 306 844-1532.

**Short Title:** Cost Analysis of Malignant Pleural Effusions

## Conflict of Interest Statement

Dr. Miller reported receiving support for lectures on HIV infection from Merck and Gilead. Dr. Rahman reported that he acts as a consultant to Rocket Medical for device development. No other conflicts of interest were reported.

## Funding Information

The TIME2 trial was supported with an unrestricted education grant from the British Lung Foundation and the Robert Luff Foundation, London, England. The University of Oxford sponsored the TIME2 trial. The IPCs and drainage bottles were provided by Rocket Medical, Washington, England. An Alberta Innovates Health Solutions Clinician Fellowship award supported Dr. Penz during her involvement in the analysis and preparation of the manuscript. Dr. Manns is supported by Alberta Innovates – Health Solutions salary award and by an alternative funding plan from the Government of Alberta and Universities of Alberta and Calgary. No additional funding was provided for this study.

**Abstract Presentation and Publication**

E. Penz, E. Mishra, H. Davies, B. Manns, N. Rahman Comparing the Cost of Talc Pleurodesis vs. Indwelling Pleural Catheter For Malignant Pleural Effusions: A Detailed Cost Analysis Done Alongside A Randomized Clinical Trial. Am J Respir Crit Care Med 187;2013:A2152. American Thoracic Society Poster Presentation and Discussion. Philadelphia, Pennsylvania, United States May 19, 2013.

*Key words:* Key Words: Pleural Effusion, Malignant, Cost and Cost Analysis, Palliative Care, Pleural Disease

Abstract

## Background

Malignant pleural effusion is associated with short life expectancy and significant morbidity. A recent randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis found that indwelling pleural catheters reduced time in hospital and need for additional procedures but were associated with excess adverse events.

## Methods

Using data from the clinical trial, we compared costs associated with use of indwelling pleural catheters and with talc pleurodesis. Resource use and adverse events were captured through case report forms over the 1-year trial follow up. Costs for outpatient and inpatient visits, diagnostic imaging, nursing and doctor time were obtained from the NHS reference costs and University of Kent's Unit Costs of Health and Social Care 2011 and inflated to 2013 using the UK Consumer Price Index. Procedure supply costs were obtained from the manufacturer. Difference in mean costs was compared using non-parametric bootstrapping. All costs were converted to US dollars using the OECD Purchasing Power Parity Index.

## Results

Overall mean cost (SD) for managing patients with indwelling pleural catheters and talc pleurodesis was $4993 (5529) and $4581 (4359) respectively. The incremental mean cost difference was $401 with a 95% CI (-1387 to 2261). The mean cost related to ongoing drainage in the indwelling pleural catheter group was $1011 (732) versus $57 (213) in the talc pleurodesis group (p=0.001). This included the cost of drainage bottles, dressing changes in the first month and catheter removal. There was no significant difference in cost of the initial intervention or adverse events between the groups. For patients with

survival less than 14 weeks, IPC is significantly less costly than talc pleurodesis with mean cost difference of -$1719(95% CI -3376 to -85).

## Conclusion

There is no significant difference in mean cost of managing patients with indwelling pleural catheters compared with talc pleurodesis. For patients with limited survival, IPC appears less costly.

**Trial Registration:** isrctn.org Identifier: ISRCTN87514420

## INTRODUCTION

Malignant pleural effusion accounts for 22% of all pleural effusions with over 150,000 cases diagnosed annually in the United States and more than 1 million worldwide.[1, 2] British Thoracic Society guidelines recommend that graded talc slurry be used as the sclerosing agent of choice delivered via an intercostal tube as first line management for patients with malignant pleural effusion (herein referred to as talc pleurodesis); indwelling pleural catheter (IPC), or tunneled pleural catheter, insertion is recommended for a select subgroup. The delivery of the two interventions differs - talc pleurodesis requires upfront hospitalization, whereas IPC insertion, in general, is performed in an outpatient setting with ongoing drainage in the community thereafter.

The effectiveness of IPC insertion and talc pleurodesis has been compared in a recent randomized trial. The TIME2 trial measured symptom control, the subjective relief of malignant pleural effusion related dyspnea, with both treatment modalities.[3] Secondary outcomes of the TIME2 trial included quality of life and health care costs. Although IPCs were not found to be superior to talc pleurodesis for relieving dyspnea or improving quality of life, the use of IPCs was associated with reduced hospital stay and decreased pleural procedures, though with more frequent adverse events. The only other randomized controlled trial comparing safety and efficacy of IPC insertion and pleurodesis for malignant pleural effusion used doxycycline as the sclerosant.[4] In this study of 144 patients, there was no difference in effusion recurrence rate at 30 days, improvement in dyspnea or quality of life; however, there was a significantly shorter length of hospital stay in the IPC group.

Given the unknown impact of IPCs on resource use and costs, relative to standard care (i.e. talc pleurodesis), a more thorough analysis of costs is warranted prior to recommendation of the adoption of IPC use as first line management for patients with malignant pleural effusion.

## METHODS

### Objective and Overview

Using clinical and resource data captured in the TIME2 trial, our primary objective was to compare total costs associated with the use of IPCs and with talc pleurodesis in patients with malignant pleural effusion. In a secondary analysis, we sought to compare the costs between groups across different categories (the initial procedure, adverse events and those related to ongoing drainage).

TIME2 was a randomized controlled trial, conducted in 7 centers across the UK, of 106 patients with confirmed malignant pleural effusion who were randomized to either IPC insertion or talc pleurodesis. Ethical and regulatory approval for the study was obtained from the Milton Keynes research ethics committee before recruitment commenced (REC number: 07/Q1603/2). After written informed consent, patients were randomized to receive either talc (chest tube and talc slurry pleurodesis) or IPC (Rocket Medical). IPCs were inserted in the outpatient setting (unless the patient was already admitted to hospital at the time of randomization in which case the catheter was inserted in hospital). Patients and their caregivers were instructed on how to perform drainage from the catheter. On average, the frequency of IPC drainage in the first 6 weeks of the trial was twice weekly although this varied and was recorded in case report forms throughout the trial. All patients randomized to talc pleurodesis had a chest tube inserted and

talc pleurodesis performed, if appropriate, in hospital. Primary objective of the trial was to compare the efficacy of IPCs and talc pleurodesis at relieving dyspnea using the 100 mm visual analog scale. Baseline characteristics of the patients are summarized in Table 1.

We conducted a cost analysis alongside the clinical trial. The perspective adopted for the valuation and costing of the intervention was that of the health care payer, therefore non-medical costs (i.e. patient time and travel costs, as well as costs related to lost productivity) were not included. All patients were followed for 1 year or until death, whichever occurred first, and the costing analysis was performed over the same time frame. The median life survival in this patient population was 200 days (14% were alive at 1 year) therefore no additional modeling of costs beyond the trial period was performed. Given that costs included in the analysis were incurred over the trial follow-up period (<= 1 year), discounting was not performed.

**Resources and Costs**

The resources required to manage malignant pleural effusion was based on information documented on trial patients' case report forms. Resource use throughout the trial was recorded throughout the study period and divided into the following categories: (1) initial intervention procedures and hospital length of stay (if required), (2) resources related to ongoing drainage and (3) adverse events, and are summarized in Table 2.

Initial Intervention

Initial intervention costs consisted of baseline chest tube insertion costs plus hospital or day case unit charges, depending on whether patients were treated as an inpatient or outpatient. Baseline insertion costs included chest tube insertion supplies, ultrasound provision, nursing time (1hr),

physician time (1hr) and drainage (i.e. if additional collection bottles were used for patients with high volume fluid production). In the case of patients with an IPC, we included an additional cost for IPC education by a nurse (duration 2 hours). For patients undergoing talc pleurodesis, in addition to baseline insertion costs, we included costs related to the pleurodesis itself (i.e. analgesia and the need for an additional pre-pleurodesis chest radiograph).

On-going Drainage

The total volume of pleural fluid drainage was recorded in both study groups. Patients with IPCs were given a logbook after insertion of their catheter in which they were asked to record how often they drained their IPC and the number of bottles required. The total number of bottles used during the follow up period was then multiplied by the manufacturer's acquisition cost for the drainage bottle.

Adverse Events

Data for all adverse events were collected. A blinded reviewer (Dr. Robert Miller MBBS FRCP) determined if adverse events were related to the intervention. Resource use and any additional procedure required as a result of an adverse event were recorded and assigned a specific procedural cost. Diagnostic imaging associated with the adverse event was also noted. Finally hospitalizations (including the length of stay) and the number of outpatient visits associated with each adverse event were recorded.

**Valuation of Resource Use**

All patients admitted to hospital were assigned a cost of hospital care using the Health Resource Group (HRG) 'Pleural Effusion with major co-morbidities and complications', taken from the UK National Health Service (NHS) HRG reference manual.[6] This HRG cost was converted to a daily hospital cost using information on average length of stay for this Health Resource Group

(average length of stay = 7.7 days). We then calculated a total hospitalization cost for patients based on their individual length of stay. An excess bed day cost, lower than the daily hospital cost noted above, was then incorporated to acknowledge the fact that the cost of hospital admissions tends to decrease as the number of days increases beyond a 'trim point' (13 days).[6]

For outpatient visits, a HRG specific day-case unit cost was obtained from the NHS reference cost manual. Nursing and physician charges were taken from the University of Kent's Unit Costs of Health and Social Care 2011.[7] Price weights for supplies associated with the procedures were obtained directly from the manufacturer. All unit price weights are summarized in Table E1 of the online data supplement.

Costs in 2011 UK pounds were inflated to 2013 values using the UK Consumer Price Index (CPI).[8] Using the OECD Purchasing Power Parity Index (Dec 2012), costs in UK pounds were converted to 2013 US dollars.[9]

**Statistical Analysis**

All analyses were calculated on an intention to treat basis. Cost data is not normally distributed (typically right-skewed with heavy tail); therefore to compare mean costs across groups, our primary analysis used non-parametric bootstrap with 1000 replications to derive a 95% confidence interval for the incremental mean cost difference between the two groups. For the bootstrap estimate, we used the percentile method. We randomly sampled with replacement, generating 1000 random samples. Differences in mean costs for each of the 1000 samples was calculated, ranked from lowest to highest and difference in mean cost for the $26^{th}$ and $975^{th}$ ordered values defined the 95% confidence interval.

The data collection was incomplete for one main variable: the total drainage volume. To account for this, drainage volume following the initial procedure was imputed based on the mean drainage of complete cases for each group.[10] Missing values for drainage volume during the follow up period were imputed using last drainage carried forward as there was significantly higher inter-patient variability in drainage compared with intra-patient variability across follow up periods. The proportion of drainage data missing is described further in Table E2 of the online data supplement.

All statistical analyses were performed using Stata 11.2.

Sensitivity Analysis

To test the robustness of our base case assumptions, we performed several sensitivity analyses. Firstly, procedural costs (i.e. for chest tube insertion supplies plus nursing and physician time) may have been included within the NHS unit price weights given for outpatient visits or inpatient stays in the NHS reference manual. Therefore, we explored the impact of the cost analysis after removing all additional procedural costs from the day case unit and inpatient unit price weights.

Secondly, our estimates of total costs did not include follow up visit costs mandated by the trial protocol as these were deemed to be equal between both groups. As part of our sensitivity analyses, we compared mean total costs between the groups including all clinical trial protocol-related costs.

Thirdly, we adjusted the price of IPC drainage bottles to see if that affected the total mean cost difference between groups.

Fourthly, there is some suggestion in the literature that the cost-effectiveness of IPC is greater in patients with limited life expectancy (< 3months).[11] We compared the mean cost difference between groups in patients who survived longer than 14 weeks as well as in patients who died within 14 weeks of randomization within the trial.

Lastly, our primary analysis assumed that patients or their families in the IPC group performed all drainage of the pleural catheters. As part of our sensitivity analysis we assumed that patients with an IPC would require 2 hours of nursing care per week and compared the mean cost difference between groups under this scenario.

## RESULTS

### Baseline Characteristics

Baseline characteristics between the two groups were similar (Table 1).[3]

### Primary Outcome, Adverse Events and Mortality

All primary and secondary clinical outcomes are reported separately.[3] A limited summary of the primary clinical outcome, adverse events and survival time from the clinical trial are reported in Table 3. There was no difference in the primary clinical outcome of mean daily dyspnea over the first 42 days of the trial between groups. There was no significant difference in survival time between groups with a mean difference of -0.8months (95% CI, -2.4 to 0.8 months; p=0.32). Overall, 21 of 52 patients (40%) in the IPC group vs 7 of 54 patients (13%) in the talc group

experienced adverse events (OR, 4.70; 95% CI, 1.75-12.60; P=.002); however, no significant difference was seen between groups with serious adverse events.

**Resource use**

Average resource use by each group is summarized in Table 4. The distribution of total costs in each group is shown in Figure 1.

Initial Procedure

101 drains were successfully inserted, 51 in the IPC arm and 50 in the talc pleurodesis arm (2 patients died between randomization and enrolment therefore no procedures were performed, 2 patients had no pleural fluid, 1 patient withdrew from the study). All patients randomized to talc pleurodesis were admitted to hospital while 19 patients (37%) randomized to the IPC group were inpatients at the time of randomization and had their IPC placed in hospital.

In the talc pleurodesis group 10 patients' (18.5%) and in the IPC group, 23 patients' (44%) data were missing. The average initial drainage was 2825ml (SD 1991ml) in the talc pleurodesis group, equivalent to 2 large drainage bottles (1800ml capacity); and 1776ml, equivalent to 2.96 bottles with 600ml capacity (SD 1.04), in the IPC group.

Following insertion of the catheter, the mean length of hospital stay (LOS) in the IPC group was 2.49 days (SD 7) with a median of 0 days (IQR 0-1) after randomization. Mean LOS in the talc pleurodesis group was 4.98 days (SD 3.65) with a median LOS of 4 days (IQR 2-6) after randomization: a difference of - 2.5 days (95% CI: -4.68 to -0.292). For patients in the IPC

group already admitted to hospital at the time of randomization (N=19), mean LOS after randomization was 6.63 days (SD 10.3) with a median of 2 days (IQR 1-8).

Follow up drainage

Average pleural drainage for the study period was 24.8 bottles (SD 21) in the IPC group and 1.6 bottles (SD 7) in the talc pleurodesis group. Due to re-accumulation of patients' pleural effusions (i.e. pleurodesis failure) 46 additional procedures were performed on 12 patients in the talc pleurodesis group. This compared to three additional procedures on 3 patients in the IPC group. Seven out of 54 patients (13%) in the talc pleurodesis group required repeat thoracentesis versus one patient in the IPC group. Ten patients in the talc pleurodesis group and 2 patients in the IPC group required further chest tube insertion during the trial.

Adverse Events

There were a total of 28 adverse events in the IPC group and 9 adverse events in the talc pleurodesis group. In the IPC group, these resulted in 33 outpatient visits (n=17) and 15 admissions to hospital (n=11) with an average length of stay of 8.86 days (SD 12). In the talc pleurodesis group there were 41 additional outpatient visits (n=12) and 15 admissions to hospital (n=10) with an average length of stay of 5.46 days (SD 4 days).

**Costs**

Primary Analysis

Mean costs for each group and the mean cost difference between groups are summarized in Table 4. The total mean cost (SD) for managing patients with IPC and talc pleurodesis was $4993(5529) and $4581(4359) respectively, with a mean difference of +$401 (95% CI -1387 to

2261). There was no significant difference in mean adverse event cost between groups nor was there a difference in significant mean cost between groups after combining the cost of initial intervention and ongoing drainage costs over the trial period.

**Sensitivity Analysis**

Results of the sensitivity analyses are shown in Table 5.

After removing the procedural costs from patient visits (i.e. including just the day-case visit or hospital cost in the cost calculation), the mean cost difference between groups was not significant, -$54 (95% CI -1565 to 2122).

Inclusion of clinical trial protocol-induced costs altered the mean total cost in each group however the difference between groups was not significant.

We tested whether incremental reductions in the manufacturer's price for IPC drainage bottles (by 75%, 50% or 25%) had any effect on the total mean cost noting a trend towards cost savings with IPC; however, the confidence intervals around the estimates remained large and included a mean cost difference of zero.

The mean cost of treating patients who survived for more than 14 weeks was $5707(1122) and $4625(1085) in the IPC and talc pleurodesis groups, respectively (mean difference $1098 (95% CI -1418 to 4010)). For patients who died before 14 weeks, the mean cost of treating patients was lower in the IPC group ($2944(656)), compared with the talc pleurodesis group (($4671(642)) (mean difference -$1719(95% CI -3376 to -85)).

If we assume that patients with IPCs require nursing care of 2 hours per week for drainage and dressing changes, the mean cost for the IPC group increases to $6807(6225) and to $4638(4411) in the talc pleurodesis group resulting in a significant difference in costs of $2130 (95% CI 205 to 4184).

## DISCUSSION

Using a comprehensive costing dataset collected alongside a randomized trial over a 1 year period, we noted no difference in the cost of treating patients with malignant pleural effusion with first line IPC insertion compared with talc pleurodesis. The talc pleurodesis group had a longer initial length of hospital stay but there were significantly higher costs associated with ongoing drainage for patients with an IPC. Results from our sensitivity analyses suggest that IPC is a less costly alternative to talc pleurodesis in patients with limited survival. Alternatively, if patients with IPC require significant nursing support for ongoing drainage (2 hours per week or more), then IPC use is more costly compared to talc pleurodesis.

The TIME2 trial demonstrated that both IPC and talc pleurodesis are effective in reducing patient-reported dyspnea symptoms in patients with malignant pleural effusions and concluded that the use of either IPC or talc pleurodesis should be based on patient preferences after discussion of the risks and benefits of each therapy. This cost analysis shows no difference in overall costs between IPC and talc pleurodesis, lending support to the clinical recommendation that either IPC or talc pleurodesis can be used to treat malignant pleural effusions and that the choice of which one should be based on patient preferences, after discussion of the risks and

benefits of both therapies. In addition to patient preferences, and when considering the costs of these two treatment options from the healthcare payer perspective, we offer the following recommendations:

1. If on average, patients will require 2 or more hours of nursing care per week for drainage and catheter care, then IPC becomes significantly more costly and we recommend talc pleurodesis be considered the preferred treatment option for patients with malignant pleural effusions.
2. For patients with expected survival less than 14 weeks (based on a proxy performance status score of 3 or 4), and without expected nursing support at home, we recommend IPC be considered the preferred treatment option for patients with malignant pleural effusions.
3. For patients with expected survival less than 14 weeks and with expected nursing support of 2 or more hours/week, there is no significant cost difference between IPC and talc pleurodesis and therefore the choice of intervention should be based solely on patient preferences after informed consent.

To date, no other study that we are aware of has compared the costs associated with IPC or talc pleurodesis using data from a randomized clinical trial. Other studies, which have modeled the cost effectiveness of IPCs using observational data, show IPCs to be incrementally more costly than talc pleurodesis.[11, 12] In one study, IPC insertion was noted to be cost-effective relative to talc pleurodesis when the life expectancy of patients was less than 6 weeks or if the probability of spontaneous pleurodesis with IPC was greater than 87%.[12]

More recently, a cost-effectiveness decision model of tunneled pleural catheters versus bedside pleurodesis, repeated thoracentesis and thoracoscopic talc pleurodesis found the former to be superior to the other therapeutic options. An incremental cost-effectiveness ratio (cost per quality adjusted life year) of $49,978 relative to repeat thoracentesis was demonstrated.[11] The findings of Puri *et al* however, were specifically in patients with limited longevity (survival less than 3 months), a spontaneous pleurodesis rate from IPCs of 40% and a complication rate of 5%. If spontaneous pleurodesis rates fell or complication rates increased the cost-effectiveness of IPC reduced. When patient survival was modeled to 12 months bedside talc pleurodesis was superior to all other strategies.

These results support our findings that, in a patient population with a median survival of approximately 6 months, IPCs have a similar cost to bedside talc pleurodesis. Of note, our study suggests that the use of IPC may be associated with cost savings, compared to talc pleurodesis for patients who survived <14 weeks. To our knowledge, there have been no studies published to date that have identified predictors of mortality in patients with malignant pleural effusion. This clinical information may be very helpful in identifying patients for whom the use of IPC is clinically indicated and ultimately cost-effective.

A major strength of our study was the comprehensive and complete collection of resource data for patients in the trial. In addition, as our study population has a limited life expectancy (median 6 months) the length of follow up for one year was sufficient to capture all clinically important outcomes and relevant costs associated with the intervention.[3]

There are several limitations of our study. First, the sample size was chosen to determine a clinically important difference in breathlessness between the groups and was not powered to detect differences in health care costs. Despite this, our study provides relevant information about the cost of both therapies. Second, while it may be advantageous that all costs incurred during the period of a clinical trial are included (regardless of whether they are related to the intervention (e.g. all hospitalizations versus intervention related-hospitalizations)), we evaluated costs specific to the intervention only. Third, the perspective of our study was that of the healthcare system. Whilst this perspective is admittedly narrower than other possible perspectives (for example, societal perspective, which attempts to capture time costs of patients, caregiver burden costs and costs associated with productivity loss), the additional costs required to inform a societal perspective were not collected during the clinical trial. Fourth, the overall IPC adverse event rate reported in the TIME2 trial was 40% compared with 13% in the talc pleurodesis group, higher than what has been described previously in the literature. We believe this may be related to a few factors: most data in the literature has been retrospective and therefore actual complications recorded may be lower; and definition of adverse events vary (the TIME2 trial counted IPC blockage as a complication compared to other studies which did not). For costing purposes in our study, additional procedures required during the trial and related adverse events were combined. Despite the increased number of patients with adverse events in the IPC group, the costs associated with adverse events were no different between groups. This likely is related to the fact that serious adverse events were not significantly different between the groups and additional costs associated with increased pleural procedures in the talc group were balanced out by the increased total number of adverse events in the IPC group. Finally, this study examined the differences in costs between two management approaches with similar

effectiveness(i.e. a cost minimization study). A full economic evaluation incorporating quality of life and costs would be informative to determine the cost-effectiveness of IPCs. This evaluation is underway.

## CONCLUSION

The overall comparative costs of managing patients with malignant pleural effusion with IPCs or talc pleurodesis are similar however; the resources required for the two strategies differ. Higher initial hospital bed-day costs are incurred with talc pleurodesis whereas IPC insertion results in increased ongoing drainage costs. IPCs become less costly compared to talc pleurodesis for patients with expected survival less than 14 weeks. Identifying predictors of survival in patients with malignant pleural effusions may be helpful in deciding which management strategy may be best for patients. Cost savings with IPC may be lost if significant nursing support is required (>2hours per week). These findings are important for both clinicians and healthcare decision makers. With the information available we suggest that first-line management of patients with malignant effusion can include either treatment and the choice of patients' treatment should be tailored to individual circumstances and goals of care.

## ACKNOWLEDGEMENTS

We thank Peter Faris, PhD, Alberta Health Services, Calgary, Canada and Brennan Kahan, MRC Clinical Trials Unit, London, UK for helpful discussions regarding statistical analysis.

### Author Contributions

Study concept and design: EM, HD, NR

Acquisition of data: EM, HD, NR

Analysis and interpretation of data: EP, EM, HD, BM, RFM, NR

Drafting of manuscript: EP, BM

Critical revision of manuscript for important intellectual content: EP, EM, HD, BM, RFM, RFM

Statistical analysis: EP, BM

Approval of final version: EP, EM, HD, BM, RFM, NR

Integrity of analysis and manuscript: EP, NR affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

**Conflict of Interest Statement**

Dr. Miller reported receiving support for lectures on HIV infection from Merck and Gilead. Dr. Rahman reported that he acts as a consultant to Rocket Medical for device development. No other conflicts of interest were reported.

**Funding Information**

The TIME2 trial was supported with an unrestricted education grant from the British Lung Foundation and the Robert Luff Foundation, London, England. The University of Oxford sponsored the TIME2 trial. The IPCs and drainage bottles were provided by Rocket Medical, Washington, England. An Alberta Innovates Health Solutions Clinician Fellowship award supported Dr. Penz during her involvement in the analysis and preparation of the manuscript. Dr. Manns is supported by Alberta Innovates – Health Solutions salary award and by an alternative funding plan from the Government of Alberta and Universities of Alberta and Calgary. No additional funding was provided for this study

Table 1. Baseline demographic data for 106 patients with malignant pleural effusion

| | IPC | Talc |
|---|---|---|
| **Total no.** | 52 | 54 |
| **Age, mean (SD), y** | 67 (11) | 67 (12) |
| **Male:female (%male)** | 23:29 (44) | 23:31 (43) |
| **Type of malignancy:** | | |
| **breast** | 16 | 11 |
| **lung** | 9 | 16 |
| **mesothelioma** | 6 | 5 |
| **other** | 21 | 21 |
| **VAS dyspnea, mean (SD), mm** | 62 (22) | 55 (26) |
| **VAS chest pain, mean (SD), mm** | 29 (30) | 22 (29) |
| **Size of effusion on chest radiograph, % hemithorax (SD)** | 51 (23) | 49 (25) |
| **EORTC QLQ-30: global health status % (SD)** | 37 (23) | 37 (20) |
| **Inpatient:outpatient at enrolment (% inpatient)** | 19:33 (35) | 22:31 (42) |

Davies HE, Mishra EK, Kahan BC, et al. JAMA 2012;307(22):2383-2389. Permission to reproduce received from JAMA.

VAS = visual analogue scale, EORTC QLQ-30 = European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (higher % means better quality of life). Other malignancies were colorectal (4 IPC:3 talc), ovarian (2 IPC:5 talc), adenocarcinoma of unknown primary (4 IPC: 2 talc); renal (3 IPC: 2 talc); sarcoma (1 IPC, 2 talc); thymoma (1 IPC, 1 talc); oesophageal (2 IPC); peritoneal (1 IPC, 1 talc); prostate (1 IPC); ampullary (1 IPC); leiomyosarcoma (1 IPC); melanoma (1 talc);

myeloma (1 talc); nasopharyngeal (1 talc) and unknown (1 IPC, 1 talc). 1 patient in the talc group died prior to enrolment so no demographic data was available.

**Table 2. Resource Use Categories**

| COST CATEGORY | RESOURCE USE | MEASUREMENT |
|---|---|---|
| Initial Intervention | | |
| | Procedure | Includes procedure supply costs, ultrasound, nursing time(1hr), physician time(1hr) and drainage volume(if additional bottles used for high volume drainage), plus<br>IPC group – IPC education by Nurse(2hrs)<br>Talc group – talc pleurodesis supplies |
| | Hospitalization or Day Case Unit | LOS documented in hospital chart and recorded in CRF – calculated as discharge date minus enrolment date.<br>For IPC patients treated as outpatient, daycase unit visit was recorded |
| Ongoing Drainage | | |
| | Drainage requirements | Number of drainage bottles used by IPC patients was recorded in CRF<br>Drainage assumed to be performed by patient |
| Adverse Events | | |
| | Severity & Inpatient vs. Outpatient | Nature of adverse event was recorded in the CRF, whether it required inpatient or outpatient management and LOS |
| | Diagnostic Imaging | Imaging associated with an adverse event was recorded in the CRF |
| | Procedures | Procedures related to adverse events were documented in the CRF |
| IPC = indwelling pleural catheter; CRF = case report form; LOS = length of stay | | |

**Table 3. Summary of primary outcome, adverse events and mortality from TIME2 randomized clinical trial**

| | IPC | Talc |
|---|---|---|
| **Primary Outcome** | | |
| VAS daily dyspnea over 42 days, mean (95% CI), mm | 24.7 (19.3 to 30.1) | 24.4 (19.4 to 29.4) |
| Difference in mean daily dyspnea, mean (95% CI),mm | 0.16 (-6.82 to 7.15; p=0.96) | |
| VAS change in dyspnea from baseline, mean decrease (95% CI), mm | 37.0 (29.2 to 44.8) | 30.2 (22.0 to 38.4) |
| **Adverse Events*** | | |
| **Serious, total number** | **9** | **5** |
| Pleural infection | 5 | 1 |
| Cellulitis | 1 | 0 |
| Symptomatic fluid loculation requiring fibrinolytic | 1 | 1 |
| Catheter site metastases | 0 | 0 |
| Catheter blockage | 1 | 1 |
| Other † | 1 | 2 |

| | | |
|---|---|---|
| **Nonserious, total number** | **19** | **4** |
| Pleural infection | 2 | 0 |
| Cellulitis | 5 | 1 |
| Symptomatic fluid loculation requiring fibrinolytic | 2 | 0 |
| Catheter site metastases | 1 | 0 |
| Catheter blockage | 9 | 0 |
| Other | 0 | 3 |
| **Mortality** | | |
| Median survival, days (IQR) | 153 (73 to 288) | 200 (39 to 392) |

*Adapted from JAMA 2012;307(22):2383-2389. Permission from JAMA received.*

Abbreviations: IPC = indwelling pleural catheter, VAS = visual analogue scale, IQR = interquartile range

*Total number of adverse events is listed. A patient may have had more than 1 adverse event.

†The serious adverse events included in the "Other" category were chest pain requiring readmission (1 IPC), surgical emphysema (1 talc), persistent air leak (1 talc). The 3 nonserious adverse events in the talc group were all chest tube displacement prior to pleurodesis. The complications of symptomatic fluid loculation requiring fibrinolytics, cellulitis, and blocked catheter in the talc group were observed in 2 patients who had IPCs inserted following failure of pleurodesis.

**Table 4. Resource Use, Mean Cost & Mean Cost Difference between IPC and Talc in US$**

| CATEGORY | IPC | | Talc | |
|---|---|---|---|---|
| | Resources Used | Cost Mean(SD) | Resources Used | Cost Mean(SD) |
| Initial Intervention | | | | |
| Intervention procedures | 51 | $797(36) | 53 | $476(47) |
| Mean length of stay in days* | 2.49(7)<br>N=51 | $1147(2961) | 4.98(4)<br>N=51 | $2461(1834) |
| Day Case Visit | 32 visits | $325(260) | 0 visits | $0 |
| **Total Initial Intervention Costs** | **$2276(2849)** | | **$2939(1844)** | |
| | | | | |
| **Total Ongoing drainage Costs** | **$1011(732)** | | **$57(213)** | |
| Adverse Events | | | | |
| Outpatient visits† | 33 | $336(694) | 41 | $401(1440) |
| Inpatient visits† | 15 | $1188(4453) | 30 | $871(2327) |
| Procedures† | 3 | $19(76) | 46 | $227(694) |
| Diagnostic Imaging‡ | 34<br>6 | $43(106) | 66<br>2 | $52(137) |

| | | |
|---|---|---|
| **Total Adverse Events Costs** | **$1653(4693)** | **$1555(3737)** |
| **Total Cost** | **$4993(5529)** | **$4581(4359)** |
| | | |
| DIFFERENCE IN COSTS | | |
| TOTAL COST[ll] | | |
| Mean difference§<br><br>95% CI | $401<br><br>(-1387 to 2261) | |
| ADVERSE EVENTS COST[ll] | | |
| Mean difference§<br><br>95% CI | $76<br><br>(-1524 to 1786) | |
| COMBINED INITIAL INTERVENTION & ONGOING DRAINAGE COST[ll] | | |
| Mean difference§<br><br>95% CI | $316<br><br>(-603 to 1426) | |

*Mean length of stay associated with insertion of initial intervention (includes those who were not admitted in the IPC group)

†Total number of visits or procedures performed in each group

‡Total number of chest x-rays (top) and CT scans (bottom) performed in each group

§IPC minus Talc

llBootstrap estimate of mean cost difference and 95% confidence interval

**Table 5. Impact of changes in uncertain variables on mean cost differences**

| | MEAN TOTAL COST | | MEAN COST DIFFERENCE | |
|---|---|---|---|---|
| | IPC | Talc | (IPC - Talc) | |
| REDUCTION IN PRICE OF BOTTLES | | | | |
| Original price* | $4993(5529) | $4581(4358) | $401(95% CI -1387 to 2261) | |
| 25%† | $4444(5491) | $4463(4038) | -$43(95% CI -1745 to 1802) | |
| 50%‡ | $4255(5425) | $4450(4016) | -$221(95% CI -1890 to 1612) | |
| 75%§ | $4059(5360) | $4439(3996) | -$404(95% CI -2038 to 1412) | |
| COST OF PROCEDURES REMOVED FROM PATIENT VISITS | | | | |
| | $3898(5187) | $3919(3612) | -$54(95% CI -1565 to 1798) | |
| CLINICAL TRIAL PROTOCOL COSTS INCLUDED IN TOTAL COSTS | | | | |
| | $5406(5554) | $5106(4146) | $270(95% CI -1582 to 2122) | |
| SURVIVAL | | | | |
| Alive >14 weeks | $5707(1122) | $4625(1085) | $1098(95% CI -1418 to 4010) | |
| Alive <= 14 weeks | $2944(656) | $4671(642) | $-1719(95% CI -3376 to -85) | |
| NURSING CARE REQUIRED FOR IPC DRAINAGE | | | | |
| 1/week drainage (2hrs) | $6807(6225) | $4638(4411) | $2130(95% CI 205 to 4184) | |
| 1/week drainage (1hr) | $5838(5840) | $4600(4337) | $1202(95%CI -661 to 3134) | |
| Bottle price | | | | |
| First 4 weeks | *$40.13 | †$29.97 | ‡$20.11 | §$10.02 |
| > 4 weeks | *$28.11 | †$21.06 | ‡$14.20 | §$7.02 |

## References

1 Ferlay J, Bray F, Forman D, et al. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 08/10/2012.

2 American Thoracic Society. Management of malignant pleural effusions. *Am J Respir Crit Care Med.* 2000;**162**(5):1987-2000.

3 Davies H, Mishra E, Kahan B, 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.

4 Putnam JJ, Light R, Rodriguez R, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. *Cancer.* 1999;**86**(10):1992-1999.

5 Penz ED, Mishra EK, Davies HE, et al. Comparing the Cost of Talc Pleurodesis vs. Indwelling Pleural Catheter for Malignant Pleural Effusions: A Detailed Cost Analysis done Alongside a Randomized Controlled Trial [abstract]. *Am J Respir Crit Care Med.* 2013;**187**:A2152.

6 Department of Health. 2010-11 Reference costs publication[Internet]. London, UK: Department of Health; 17/11/2011. Available from: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_131140, accessed 16/07/2012.

7 Personal Social Services Research Unit. Unit Costs of Health and Social Care 2011[Internet]. Canterbury, UK: University of Kent; 2011. Available from: http://www.pssru.ac.uk/pdf/uc/uc2011/uc2011.pdf, accessed 16/07/2012.

8 Office for National Statistics, Prices Division. "Consumer Price Inflation Reference Tables, October 2013 (Table 2)". http://www.ons.gov.uk/ons/datasets-and-tables. Accessed December 4th, 2013.

9 OECD (2013). "Purchasing power parities for GDP", *Economics: Key Tables from OECD*, No. 11. doi: 10.1787/ppp-gdp-table-2013-10-en. Accessed December 4th, 2013.

10 White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. *Stat Med.* 2005;**24**(7):993-1007.

11 Puri V, Pyrdeck TL, Crabtree TD, et al. Treatment of Malignant Pleural Effusion: A Cost-Effectiveness Analysis. *Ann Thorac Surg.* 2012;**94**:374–80.

12 Olden, AM, Holloway R. Treatment of malignant pleural effusion: PleuRx catheter or talc pleurodesis? A cost-effectiveness analysis. *J Palliat Med.* 2010;**13**(1):59-65.

## Figure legends

Figure 1. Right Skewed Distribution of Total Cost for IPC & Talc Groups