Clinical Significance of Non-expansile Lung and Development of a Stratified Treatment Pathway in Malignant Pleural Effusion

Geoffrey Andrew Martin

MBChB MRCP(UK) (Respiratory Medicine)

Submitted in fulfilment of the requirements for the degree of Doctor of Medicine

Institute of Cancer Sciences

College of Medical and Veterinary Life Sciences

University of Glasgow

May 2021

Summary

Malignant pleural effusion (MPE) is a common and regularly debilitating complication in a wide range of cancers. MPE confers a short prognosis (3-12 months depending on the primary tumour) and efficient, enduring palliation is therefore a clinical priority. Non-expansile lung (NEL) frequently complicates definitive MPE management as it precludes successful talc slurry pleurodesis (TSP) resulting in recurrent symptoms and repeat pleural interventions. Indwelling pleural catheters (IPCs) may provide reliable symptom relief in the presence of NEL, but are not universally acceptable to patients. The aim of this thesis was to progress towards improving outcomes in MPE through the reliable detection of NEL. In Chapter 3, an observational multicentre cohort of patients with MPE diagnosed at local anaesthetic thoracoscopy identified NEL in 17-34%. Radiographic identification of NEL was subject to a high level of inter-observer variation (κ 0.38–0.51). NEL was also associated with adverse survival (HR 2.2, 95% CI 1.3–3.7), although the independence of this relationship was not externally validated. Chapter 4 presents the results of a feasibility randomised controlled trial (RCT) of a pleural elastance (P_{EL})-directed treatment pathway (Elastance-Directed IPC or TSP (EDIT management)) for symptomatic MPE. This trial, abbreviated to 'pre-EDIT', demonstrated the feasibility of this RCT design and treatment pathway in terms of recruitment rate (2.4 subjects/month), technical delivery (successful P_{EL} assessment in 13/15 (87%) and 13/13 (100%) after an early equipment update) and safety (no directly attributable serious adverse events). Finally, in Chapter 5, additional data from pre-EDIT and an embedded treatment preferences survey (TPS) were explored to optimise the proposed EDIT pathway. Only 4/17 TPS respondents (24%) would choose first-line ambulatory pleurodesis via an IPC if offered, whereas 15/17 (88%) stated they would consider a 2-stage pleural intervention process incorporating P_{EL} assessment. Motion-mode sonographic assessment performed poorly as an alternative pre-drainage NEL biomarker; adequate imaging was achieved in only 10/13 (77%) and the AUC for NEL detection was 0.595 (95%CI 0.180-1.000). Novel volumetric magnetic resonance imaging pre- and post-aspiration from pre-EDIT validated the widely adopted clinical definition of P_{EL} and further supports the use of P_{EL} as a NEL biomarker. The findings from these chapters are incorporated into a proposed design for a Phase III trial of the efficacy of EDIT management.

Table of Contents

List of Tables

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of Figures

Chapter 1

Chapter 2

Chapter 3

Chapter 4

Chapter 5

Acknowledgements

I am immensely grateful to Professor Kevin Blyth for the clinical and research opportunities afforded to me during my time at the Glasgow Pleural Disease Unit (GPDU). Without his patience, good-humoured guidance and mentorship, the research presented in this thesis would not have been possible. My thanks also go to Professor Anthony Chalmers for his supportive co-supervision.

I would like to thank NHS Greater Glasgow & Clyde for my employment as a clinical research fellow, and to Rocket Medical (UK) and The West of Scotland Lung Cancer Research Group for generously funding the Pre-EDIT study.

I am indebted to my good friend Dr Andrew Kidd for his support throughout my research fellowship. Our regular coffee and chocolate muffin breaks provided essential respite from both clinical and academic challenges.

This work could not have been undertaken without the assistance of my former GPDU colleagues Dr Selina Tsim, Jan Devlin and Laura McNaughton, radiology collaborators Drs William Hedges and Gordon Cowell, medical statistician Philip McLoone, and research nurse colleagues Patricia Clark and Diane Murray. Tricia's commitment to the delivery of Pre-EDIT and meticulous attention to detail deserve a special mention here. My sincere thanks also go to Dr John Foster, Rosie Woodward and the Glasgow Clinical Research Imaging Facility radiographers for their invaluable support in delivering the Pre-EDIT study.

It is essential for me to acknowledge all the patients who generously lent their time to the Pre-EDIT study. I cannot overstate my appreciation for their willingness to participate in spite of hugely challenging personal circumstances.

Finally, I would like to express my heartfelt gratitude to my wife Caroline and our three fantastic children Rose, Ben and Luke for their patience, love and support throughout my research tenure and beyond.

Declaration

The work presented in this thesis was undertaken during my tenure as a Clinical Research Fellow at the Glasgow Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow and at the Institute of Cancer Sciences, College of Medical and Veterinary Life Sciences, at the University of Glasgow. I was supervised by Professor Kevin Blyth and Professor Anthony Chalmers.

Except where explicitly stated otherwise, all of the work reported in this thesis was undertaken by me, with the assistance of a number of colleagues who have been acknowledged in the previous section. The statistical analysis plan for the pre-EDIT trial and subsequent sample size calculation for the proposed phase III EDIT trial were done by Mr Philip McLoone, Biostatistician at the University of Glasgow Institute of Health and Wellbeing. All remaining statistical analyses in this thesis were performed by me.

Work relating to this thesis has been published in peer-reviewed journals and presented at national and international conferences.

The writing of this thesis constitutes my own work, written solely by me.

Signed

Geoffrey Andrew Martin May 2021

List of Abbreviations

AE	Adverse event
ATS	American Thoracic Society
AUC	Area Under (Receiver Operating) Curve
BTS	British Thoracic Society
CI	Confidence interval
CMR	Cardiac magnetic resonance imaging
CRF	Case report form
CT	Computed Tomography
CUP	Carcinoma of unknown primary
CXR	Chest radiograph
DICOM	Digital Imaging and Communications in Medicine
DPM	Digital pleural manometry
ECOG	Eastern Cooperative Group
EDIT	Elastance-directed indwelling pleural catheter or talc slurry pleurodesis
FoV	Field of View
GA	General anaesthetic
GCP	Good clinical practice
ICC	Intra-class correlation coefficient
ICD	Intercostal chest drain
IPC	Indwelling pleural catheter

IPP	Intrapleural pressure
IQR	Inter-quartile range
LAR	Lateral apposition ratio
LAT	Local anaesthetic thoracoscopy
LDH	Lactate dehydrogenase
LV	Left ventricular
M-mode	Motion-mode (ultrasound)
$MaxP_{EL250}$	Highest recorded P_{EL250} within a single aspiration procedure
MDT	Multi-disciplinary team
MPE	Malignant pleural effusion
MPM	Malignant Pleural Mesothelioma
MRI	Magnetic resonance imaging
NEL	Non-expansile lung
NEL_{50}	Non-expansile lung defined as less than 50% re-expansion
NEL_{75}	Non-expansile lung defined as less than 75% re-expansion
NHSGG&S	NHS Greater Glasgow & Clyde health board
NLR	Neutrophil to lymphocyte ratio
OS	Overall survival
PDU	Pleural disease unit
P_{EL}	Pleural elastance
P_{EL250}	Rolling average pleural elastance over each 250ml aspiration volume

PIS	Patient information sheet
PS	Performance status
QEUH	Queen Elizabeth University Hospital
RCT	Randomised controlled trial
REC	Research Ethics Committee
REP	Re-expansion proportion
RF	Radiofrequency
ROC	Receiver operating characteristic
ROI	Region of interest
RPO	Re-expansion pulmonary oedema
SAE	Serious adverse event
SCC	Squamous cell carcinoma
SD	Standard deviation
TIMP1	Tissue inhibitor matrix metalloproteinase 1
TPS	Treatment preferences survey
TSI	Trial specific instruction
TSP	Talc slurry pleurodesis
TUS	Thoracic ultrasound scan
TWIST	Time-resolved angiography With Interleaved Stochastic Trajectories
VA	Visual assessment
VATS	Video-assisted thoracoscopic surgery

VATS-PD	Video-assisted thoracoscopic pleurectomy decortication
VATS-PP	Video-assisted thoracoscopic partial pleurectomy
VIBE	Volumetric interpolated breath-hold examination
V_{MRI}	Pleural cavity volume measured directly using volumetric magnetic resonance imaging
V_{OUT}	Pleural cavity volume inferred from pleural aspiration volume

Publications relating to this thesis

1. Pre-EDIT: A randomized feasibility trial of elastance-directed intrapleural catheter or talc pleurodesis in malignant pleural effusion.

   GA Martin, S Tsim, AC Kidd, JE Foster, P McLoone, A Chalmers, KG Blyth.

   Chest Dec 2019;156(6):1204-1213

2. Inter-observer variation and the prognostic significance of non-expansile lung in malignant pleural effusion.

   GA Martin, AC Kidd, S Tsim, P Halford, A Bibby, NA Maskell, KG Blyth.

   Respirology March 2020;25(3):298-304

3. Pre-EDIT: protocol for a randomised feasibility trial of elastance directed intra-pleural catheter or talc pleurodesis in malignant pleural effusion.

   GA Martin, S Tsim, AC Kidd, JE Foster, P McLoone, A Chalmers, KG Blyth.

   BMJ Open Respir Res May 2018;5(1):e000293

Presentations to Learned Societies

1. Pre-EDIT: a randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc pleurodesis (EDIT) in the management of symptomatic malignant pleural effusion without obvious non-expansile lung.

   GA Martin, AC Kidd, S Tsim *et al*

   Poster presentation of pre-EDIT design at British Thoracic Oncology Group Meeting January 2018.

   Oral presentation of final pre-EDIT trial results Winter British Thoracic Society Meeting December 2018.

2. Identification and prognostic importance of non-expansile lung following drainage of suspected malignant pleural effusion.

   GA Martin, AC Kidd, S Tsim *et al*

   Oral presentation at Winter British Thoracic Society Meeting December 2017.

Chapter 1

INTRODUCTION

1 Chapter 1: Introduction

1.1 General Introduction

Malignant pleural effusion (MPE) is a commonly encountered complication in a wide range of cancers. MPE refers to the accumulation of fluid within the pleural space which frequently leads to disabling morbidity, often in the form of significant breathlessness. It universally represents incurable disease and confers a median overall survival of only 3 to 12 months, predominately depending on the underlying tumour type. [1] Efficient and durable symptom control is therefore a priority in this patient group.

Definitive MPE management is achieved through either complete evacuation of pleural fluid followed by pleurodesis to obliterate the pleural space, or regular pleural fluid drainage using an indwelling pleural catheter (IPC). Trials have demonstrated broadly similar outcomes in relation to patient-centred end points for these approaches. [2,3] The advantages and limitations of each should therefore be taken into account when choosing the most appropriate first-line intervention. However, a key consideration is the ability of the underlying atelectatic lung to re-expand as this is a pre-requisite for successful pleurodesis. Failure of adequate lung re-expansion is termed non-expansile lung (NEL). Where significant NEL is identified, pleurodesis cannot succeed and IPC insertion represents the standard of care. [4]

NEL is encountered in up to 30% of patients undergoing MPE drainage [5] and appears to be under-represented in MPE treatment literature. [2,3] However, estimates of prevalence vary widely, largely due to the difficulty in defining NEL. Within existing clinical pathways, NEL is judged subjectively on post-drainage plain chest radiographs (CXRs). Reliable NEL identification is therefore only possible after commitment to a particular treatment strategy. As such, occult NEL is a major cause of pleurodesis failure, recurrent breathlessness and a requirement for repeat pleural procedures.

The overarching aim of this thesis is to refine the management of symptomatic MPE through the accurate recognition of NEL. Improvements in the definition of NEL *post*-drainage may improve the consistency of decision making within current clinical pathways. Additionally, a better understanding of the prevalence

and prognostic impact of NEL may inform the rational design of future MPE trials and supplement existing approaches to prognostication. Moreover, a reliable and accessible means of *pre*-drainage NEL detection would facilitate the development of an MPE treatment pathway stratified by the presence or absence of NEL. Such a strategy might allow patients with expansile lung to benefit from the advantages of pleurodesis, while protecting those with NEL from the inconvenience and risks of treatment failure. Elevated pleural elastance (P_{EL}), calculated from pleural manometry data obtained during thoracentesis, is the most extensively cited pre-drainage NEL biomarker. The potential role for P_{EL}-directed definitive MPE management (ICD vs IPC) is explored for the first time in the work presented in this thesis.

This introduction describes the context in which this thesis is set including the clinical significance of MPE, its pathogenesis and current evidence-based treatment approaches. The available literature on the detection of NEL both pre- and post-drainage is reviewed, including a detailed discussion of pleural manometry techniques used to calculate P_{EL}, in order to provide a robust justification for the objectives set. Finally, an introduction to magnetic resonance imaging (MRI) as a volumetric gold standard is provided since its use has facilitated an exploration of the validity of the currently accepted definition of P_{EL}.

1.2 Malignant Pleural Effusion

1.2.1 Public health and clinical relevance

The global burden of disease relating to MPE is significant although epidemiological studies to support this assertion are sparse. Frequently cited incidence rates of 250000 and 50000 new cases of MPE each year in the United States and United Kingdom respectively, are extrapolated from a dated but rigorous attempt to identify all cases of pleural effusion in a geographically well-defined region of the Czech Republic. [6] Accepting the limitations of this approach, a typical UK district general hospital can expect to diagnose and manage around 250 cases of MPE per year. [7] With an ageing population, and therefore rising incidence of malignant disease overall, these figures are expected to rise further in coming decades.

The majority of MPEs (57%) present with breathlessness although up to a quarter may be asymptomatic and identified incidentally. [8] Cough is also commonly encountered at presentation and up to a quarter of patients may have chest pain. [8] Relief of dyspnoea is typically reported as the priority for patients with symptomatic MPE and most interventions are delivered with this intent. [9]

Despite the increasing potential for ambulatory management utilising IPCs, mean length of hospital stay associated with MPE remains greater than 5 days, which in many cases is a significant proportion of these patients' remaining lives. [10] The burden on healthcare resource is also clearly substantial; US data indicates annual hospital charges associated with MPE to be greater than $5 billion per year. [10]

1.2.2 Development of malignant pleural effusion

1.2.2.1 The pleural cavity; normal anatomy and physiology

The pleural cavity in healthy subjects is a thin (10 - 20μm), fluid-filled space in each hemi-thorax arising between visceral and parietal pleural membranes covering the lung, and lining the thoracic cage, respectively. Each pleural membrane is a smooth elastic layer of tissue formed from a superficial layer of mesothelial cells and 4 discrete deeper layers of connective tissue which also contain nerves, blood vessels and lymphatics. [11]

The purpose of the pleural cavity is poorly understood; however it appears to reduce friction between the lung and surrounding surfaces during movement associated with volume changes during the respiratory cycle. Despite this apparent function, marked variation in the structure and function of the pleura is noted between mammalian species. In particular, it is noteworthy that the adult elephant does not possess a pleural cavity, rather the pleural space is replaced by loose connective tissue in late gestation which permits an adequate degree of movement between the lung and adjacent structures. [12] This anatomical situation is analogous to that seen in humans following treatment of MPE by pleurodesis where the pleural cavity is obliterated without apparent functional deficit.

Under normal physiological circumstances, a small volume of pleural fluid, typically around 12mL in adults, [13] is maintained within each pleural cavity under slightly sub-atmospheric pressure (-3 to -5 cm H_2O) due to the elastic recoil forces of the surrounding lung and chest wall. This is produced from micro-vessel filtration of the systemic circulation, predominately within the parietal pleura, which follows a pressure gradient into the pleural cavity. Fluid is removed from the space via bulk flow into lymphatic channels which communicate with the parietal pleura through a network of lymphatic stomata. The flow rate of these lymphatic vessels has been shown to increase up to 20-fold in response to increased pleural fluid production thereby facilitating an equilibrium between pleural fluid production and removal. [14] In health, this maintains a near static pleural fluid volume however the wide surface area of the pleural cavity and resting negative pressure state readily allows large volumes of pleural fluid to accumulate if these homeostatic mechanisms are disrupted.

1.2.2.2 Pathogenesis of malignant pleural effusion

Autopsy studies suggest the majority of pleural malignancies arise from haematogenous micro-embolisation of tumour cells to the visceral pleura which in turn leads to secondary seeding to the parietal surfaces. [15] Direct invasion of the pleural cavity from tumours in the lung, chest wall or diaphragm also occurs. The exact mechanism by which pleural tumour deposits lead to MPE formation are not fully understood but both enhanced production and decreased removal of pleural fluid are likely to be implicated. [16] It is speculated that

greater pleural permeability and inflammation associated with pleural tumour may give rise to greater pleural fluid production, while lymphatic disruption, either at parietal pleural stomata or the level of distant mediastinal lymph nodes, impairs fluid removal. [16,17]

1.2.3 Breathlessness in malignant pleural effusion

Breathlessness in MPE is multifactorial and also not fully understood, however reduction in respiratory, and particularly diaphragmatic, muscle function appears to be the single most significant pathophysiological contributor to the development of dyspnoea. [18] As pleural fluid accumulates, expansion of the thoracic cage takes precedence over compression of the underlying lung parenchyma to accommodate the additional volume. The resulting outward movement of the chest wall and, most significantly, downwards displacement of the dome of the diaphragm causes a reduction in diaphragm muscle fibre length which in turn reduces its mechanical efficiency (see Figure 1.1). Greater neural drive is therefore required to achieve an equivalent degree of ventilation which is detected by mechanoreceptors throughout the respiratory system. The discordance in this situation between efferent respiratory muscle stimulation and afferent ventilatory feedback to the sensorimotor cortex (termed ‘neuromechanical uncoupling’) is thought to contribute significantly to the sensation of dyspnoea. [19] Removal of pleural fluid restores a normal chest wall and diaphragmatic conformation thus abolishing this effect even in the presence of significant NEL.

1.2.4 Underlying tumour types causing malignant pleural effusion

MPE may arise from a wide variety of tumour types. The relative prevalence of each depends on the population studied, largely due to regional variation in occupational asbestos exposure and therefore number of patients affected by malignant pleural mesothelioma (MPM). However, secondary pleural malignancy arising from carcinoma of the lung is by far the commonest cause of MPE. This is typically followed by metastatic breast cancer and then MPM. Gynaecological, renal, gastrointestinal and haematological metastases account for the bulk of remaining cases. [1]

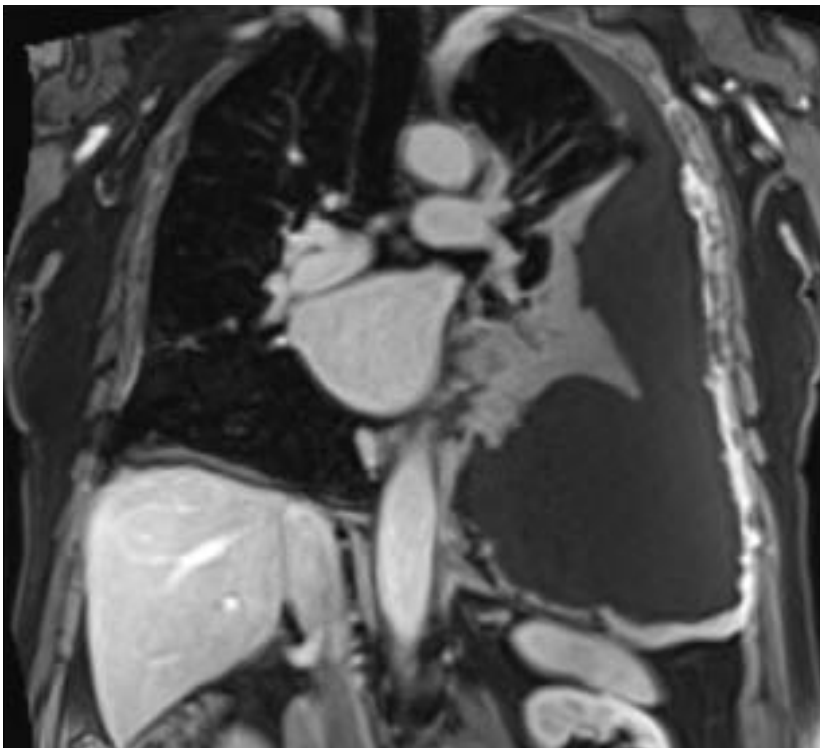


Figure 1.1 T1-weighted coronal image of a patient with a large malignant pleural effusion and inverted left hemi-diaphragm, taken post-contrast using a 3T Siemens Magnetom PRISMA® MR scanner at the Glasgow Clinical Research Imaging Facility, QEUH

Reproduced with the permission of Dr Selina Tsim.

1.2.5 Prognosis in malignant pleural effusion

Although MPE represents incurable disease, the prognosis it confers is highly variable and an essential consideration when planning palliative interventions. Underlying tumour type is well recognised as a key determinant of survival. By way of illustration, median overall survival in a large contemporary MPE cohort was 136 days but varied between only 43 days in metastatic melanoma, 74 days in lung cancer and 339 days in mesothelioma. [20] Since there is a widely differing time commitment associated with the range of palliative interventions now available, prognostication in MPE has an increasing importance in framing management discussions.

A range of MPE prognostic markers have been explored. Clive *et al* examined 14 potential variables in an international pooled cohort of unselected patients with MPE. This led to the development and subsequent external validation of the readily deployable 'LENT score' which is shown in Table 1.1. [1] More recently, Psallidas *et al* reported alternative prognostic scores derived from 25 potential clinical, radiographic and laboratory biomarkers; the 'biological' and 'clinical' PROMISE scores (see tables 1.2 (scoring system) and 1.3 (corresponding risk categories)). [21] Calculation of the biological score is impractical for routine clinic practice as it requires measurement of pleural fluid TIMP1 (tissue inhibitor of metalloproteinases 1) concentration. However, the more accessible clinical score also outperformed LENT in predicting 3-month mortality in an external validation cohort (PROMISE C-statistic 0.89 (95% CI 0·84-0·93) vs 0.75 (95% CI 0·68–0·81) for LENT). [21]

Table 1.1 The LENT prognostic score

	Variable	Score
L	**Pleural fluid LDH concentration (IU/L)** < 1500 > 1500	 0 1
E	**ECOG performance status** 0 1 2 3-4	 0 1 2 3
N	**NLR** < 9 > 9	 0 1
T	**Tumour type** Low risk • Mesothelioma • Haematological malignancy Intermediate risk • Breast cancer • Gynaecological cancer • Renal cell cancer High risk • Lung cancer • Other cancer types	 0 1 2
LDH, lactate dehydrogenase; ECOG, Eastern Cooperative Group; NLR, neutrophil to lymphocyte ratio		

Table 1.2 The clinical and biological PROMISE prognostic scores

Variable	Clinical score points	Biological score points
Previous chemotherapy		
No	0	0
Yes	4	3
Previous radiotherapy		
No	0	0
Yes	2	2
Haemoglobin (g/dL)		
>16	0	0
14-16	1	1
12-14	2	2
10-12	3	3
<10	4	4
White blood cell count (10^9 cells/L)		
<4	0	0
4-6.3	2	2
6.3-10	4	4
10-15.8	7	7
>15.8	10	9
C-reactive protein (IU/L)		
<3	0	0
3-10	3	3
10-32	5	5
32-100	8	8
>100	11	10
ECOG performance status		
0-1	0	0
2-4	7	7
Cancer type		
Mesothelioma	0	0
All other types of cancer	4	5
Lung	5	6
TIMP1 (ng/mg protein)		
<40	Not applicable	0
40-160		1
>160		2

ECOG, Eastern Cooperative Group; TIMP1, tissue inhibitor of metalloproteinases 1

Table 1.3 PROMISE score risk categories

Total points		Category	Risk of death at 3 months
Clinical score	**Biological score**		
0 – 20	0 – 20	A	<25%
21 – 27	21 - 28	B	25-50%
28 - 35	29 – 36	C	50%-75%
>35	>36	D	>75%

1.3 Malignant pleural effusion treatment options

Percutaneous removal of pleural fluid is the mainstay of symptomatic MPE management. Large volume thoracentesis, intercostal drainage and chemical pleurodesis, and IPC insertion are widely practised. Pleurodesis is typically performed via an intercostal chest drain (ICD) but may also be delivered during thoracoscopy either under sedation (local anaesthetic thoracoscopy, LAT) or general anaesthetic and single lung ventilation (Video Assisted Thoracoscopic Surgery, VATS). Historically, open drainage followed by surgical pleurectomy or pleural abrasion was also advocated for MPE control but is no longer performed outside trial settings. Each drainage method is described here in further detail.

1.3.1 Thoracentesis

Large volume thoracentesis is typically the first intervention offered to patients presenting with symptomatic suspected pleural malignancy. The procedure can be performed as a day case in ambulant patients, thus providing efficient early symptom relief and access to pleural fluid for cytological examination. In addition, post-thoracentesis radiography may occasionally reveal underlying NEL through the finding of a 'pneumothorax ex vacuo'; this concept and its significant limitations are discussed further in section 1.5.2 (page 48).

In the minority of patients in whom an underlying highly chemotherapy-sensitive malignant aetiology is identified (such as lymphoma or small cell lung cancer) early systemic treatment may obviate a requirement for further pleural intervention. [22,23] However, the majority of patients with MPE experience fluid re-accumulation and therefore an early definitive pleural intervention is recommended once histocytological confirmation (where appropriate) is completed. [4] In those patients with symptomatic MPE and a particularly poor prognosis (< 1 month), 'as required' large volume thoracentesis is a useful palliative option. [4]

1.3.2 Pleurodesis

Pleurodesis refers to the fusion of visceral and parietal pleura in order to obliterate the pleural cavity. When successfully executed, pleural fluid cannot reaccumulate and long-term symptom control may be achieved. Pleurodesis is typically achieved through the delivery of a sclerosing agent directly into the

pleural space after complete pleural drainage. As previously described, adequate lung re-expansion, and therefore pleural contact, is a prerequisite for success. The efficacy of a wide range of compounds for this purpose has been explored. Although significant study-design heterogeneity has limited direct comparisons, sterile graded talc is typically regarded as the pleurodesis agent of choice, with success rates of 70% - 100% reported in the literature. [4,5,24]

1.3.3 Method of talc delivery

1.3.3.1 Poudrage vs slurry

Intra-pleural talc may be administered either mixed with a sterile liquid (talc slurry), or insufflated as a dry powder during thoracoscopy (talc poudrage). While the former is widely available and relatively cheap to perform, historical data suggested the additional resources required for thoracoscopic management may be justifiable due to a shorter length of stay and greater pleurodesis success rates. [25] However, subsequent comparative trials have not supported this assertion. In a randomised trial of 482 patients, Dresler *et al* found no significant difference between slurry and poudrage in terms of radiological pleurodesis success at 30 days, although talc poudrage was associated with a higher rate of respiratory complications. [5] However, a *post-hoc* sub-group analysis revealed greater success with poudrage in those patients with primary lung or breast cancer compared with other underlying tumour types (82% vs 67%), thus generating further hypotheses. This study also had to be interpreted in light of the fact that poudrage treatment was delivered in a surgical setting with general anaesthesia and single-lung ventilation, and that ungraded talc was used. These factors are likely to have contributed to the complication rates reported and therefore talc poudrage delivered at physician-led LAT under conscious sedation with graded talc may be a more attractive therapeutic option. This question has subsequently been addressed directly in the recently published TAPPS trial, a UK multicentre RCT in which 330 patients were allocated to talc poudrage at LAT (n=166) or talc slurry pleurodesis (TSP, n=164). [26] Graded European talc was used in all cases. The primary outcome was pleurodesis failure within 90 days defined clinically as a requirement for repeat pleural intervention. No significant difference was observed between the groups; poudrage 22% vs TSP 24%, adjusted odds ratio 0.91 (95% CI 0.54-1.55, p=0.74). Additionally, there was no statistically significant difference in length of hospital

stay within 90 days between poudrage and TSP groups. It is therefore hard to justify purely therapeutic LAT in current clinical practice given the significant resource implications, although talc poudrage delivered at diagnostic LAT remains an efficient strategy in patients with macroscopic pleural tumour.

1.3.3.2 Chest drain size

The optimal size of intercostal chest drain (ICD) to deliver talc slurry is uncertain. Current British Thoracic Society (BTS) guidelines (under revision in 2019/20) recommend the use of small bore (10-14Fr) intercostal drains as trial evidence suggests equivalent pleurodesis success rates with these (based on radiologically-defined end points) and less pain compared with the use of large bore (24-32Fr) 'surgical' chest drains. [4] However, in the subsequently published TIME1 randomised controlled trial (RCT), small bore (12Fr) ICDs were associated with a higher rate of pleurodesis failure (30% vs 24%) than large bore (24Fr) ICDs, thus failing to meet non-inferiority criteria (difference, −6%; 1-sided 95% CI, −20% to ∞; p=0.14 for non-inferiority which was pre-specified at -15%). [27] Pleurodesis failure was robustly defined by the need for repeat pleural intervention for symptomatic MPE recurrence within 3 months. Additionally, a higher procedural complication rate was seen in those patients undergoing small bore ICD insertion (24% vs 14%, hazard ratio (HR) 1.9) although this increased rate was not statistically significant (p=0.20). [27] It is speculated that this signal may reflect a genuine increase in clinical risk due to the 'blind' nature of the Seldinger insertion technique used. These findings have yet to be independently reproduced.

1.3.4 Pleurectomy

Open pleurectomy has been historically described as a definitive treatment for symptomatic MPE but is associated with high complication and hospitalisation rates when compared to talc pleurodesis. [4] More recently, based on encouraging observational data and a speculative cyto-reductive survival benefit, partial pleurectomy delivered at minimally invasive video assisted thoracoscopic surgery (VATS-PP) was investigated as an alternative to ICD insertion and TSP for patients with symptomatic MPE secondary to MPM. [28] Despite these potential theoretical advantages, the investigators found no survival advantage associated with VATS-PP over TSP (median overall survival

13.1 months vs 13.5 months). Moreover, VATS-PP was associated with a longer hospital stay (median 7 days vs 3 days) and 31% in the VATS-PP group experienced a procedure-related complication in contrast to only 14% of those undergoing TSP. As such, pleurectomy is not recommended in routine clinical practice for any patients with symptomatic MPE. [4] However, it is hypothesised that VATS partial pleurectomy/decortication (VATS-PD) may be a useful treatment for those patients with underlying NEL since surgical removal of tumour rind may allow lung re-expansion. A pilot RCT (Meso-TRAP) comparing VATS-PD with IPC-based management of symptomatic MPE in patients with MPM and NEL is currently recruiting. [29]

1.3.5 Indwelling pleural catheters

IPCs are flexible tunnelled chest drains which facilitate regular domiciliary pleural drainage. IPCs may be inserted during a day case local anaesthetic procedure using a Seldinger technique. During insertion, IPCs are passed subcutaneously for approximately 50mm from a pleural entry site to an exit point on the lateral chest wall. They are formed from soft silicon tubing with a distal one-way valve. A Dacron cuff sited within the subcutaneous tract promotes the formation of fibrous tissue to secure the drain and minimise the risk of ascending infection. In the last decade, the wider availability of IPCs have led to a paradigm-shift in the management of patients with recurrent MPE where TSP has failed, [30] and increasingly, they facilitate first-line definitive fluid control within an ambulatory pathway. [31]

1.3.5.1 IPC drainage schedules and autopleurodesis

The principle aim of IPC drainage is to control fluid accumulation and therefore symptoms, however in a significant minority of patients, spontaneous pleural symphysis, termed autopleurodesis, may occur. [32] Drainage procedures are typically performed by community nursing teams or suitably trained patient relatives using disposable vacuum bottles. Varying drainage schedules are advocated. Aggressive daily drainage is performed in some centres based on evidence that such an approach is associated with a higher rate of autopleurodesis and therefore catheter removal. [33] In a study of 149 patients with MPE managed by IPC, autopleurodesis was achieved in 47% of those undergoing daily drainage versus only 24% in those whose IPCs were drained on

alternate days. [34] Conversely, some clinicians argue that less frequent drainage performed as required to control symptoms may reduce potential drainage-related complications and cost while achieving comparable relief of dyspnoea and improvements in quality of life. A direct comparison between daily drainage and 'as required' drainage strategies found no difference in breathlessness scores or complications, but confirmed a higher rate of autopleurodesis (37% vs 11%, hazard ratio 3·3 (95% CI 1.4–7.7)) and higher patient-reported quality of life scores associated with daily drainage. [35]

1.3.5.2 IPC advantages and limitations vs TSP

A total of 5 RCTs have now examined outcomes for patients randomised between IPC and TSP management of symptomatic MPE. [2,3,36-38] A subsequent meta-analysis found no difference in overall survival or relief of breathlessness between these strategies. [39] However, since IPC pathways direct ambulatory management, they are consistently associated with significantly reduced length of hospital stay compared with TSP, which requires initial hospitalisation. [39] Economic analyses suggest IPC insertion is more cost-effective than TSP in patients whose survival is less than 14 weeks. [40,41] However, beyond this threshold, TSP is more cost-effective due to the on-going consumable costs and district nursing time required for IPC management. Importantly, from a patient perspective, regular drainage via an IPC may provide long-term relief of breathlessness even where underlying NEL is identified. [4]

The advantages of IPC insertion must be balanced against a number of limitations, including a higher rate of clinically significant pleural infection (5-10% over the lifetime of the catheter), [2,42] the inconvenience of indwelling prosthetic material which is recognised as unacceptable to a significant proportion of patients, [43] and the requirement for an additional invasive procedure to remove the catheter if/when autopleurodesis is achieved or the catheter is no longer functioning. It is also important to recognise that the requirement to schedule daily activity around several weekly drainage sessions may be burdensome to patients, particularly where this has to be coordinated with district nursing teams who may be unable to commit to narrow appointment windows.

1.3.5.3 Outpatient pleurodesis via IPC

In some cases, outpatient pleurodesis via an IPC may combine the advantages of reduced hospitalisation with an improved chance of catheter removal. In the landmark IPC-PLUS RCT, successful talc pleurodesis at 10-weeks was reported in 35 of 69 patients (51%) in whom intra-pleural talc slurry was instilled via IPC in contrast to 19 of 70 (27%) who received 0.9% saline placebo. [44] No significant difference in adverse events (including pleural infection), length of hospital stay or mortality were seen between the two groups. [44] Ambulatory pleurodesis has also been reported in a proof of concept study utilising a silver nitrate coated IPC which in future may further simplify this process and reduce the theoretical additional infection risk from a separate procedure to instil a sclerosing agent. [45]

1.4 Summary of the current recommended approach to the management of symptomatic MPE

The most recent BTS guidance dates from 2010 and was archived in 2017. Publication of new BTS pleural guidelines are expected in 2020. In the interim, evidence-based guidance from both the American Thoracic Society (ATS) and the European Respiratory Society (ERS) have been published. [46,47] Both ATS and ERS documents acknowledge the discrete advantages and limitations conferred by TSP and IPC drainage and accept that both approaches are equally valid in patients with expandable lung. Prior to delivery of a definitive intervention, the current ATS guideline (in common with the preceding BTS 2010 guidance) recommends large volume thoracentesis to assess whether symptoms are improved by drainage and to assess underlying lung re-expansion potential (see Figure 1.2). [46] In patients with apparently expansile lung, and without a predicted ‘very short’ survival, a discussion with the patient regarding the relative risks and advantages of IPC vs TSP vs combination approaches (see Table 1.4) is recommended. [46] Thoracentesis has poor sensitivity for NEL detection (see Section 1.5.4.1) and therefore, in practice, a proportion of patients in whom an ICD is placed with a view to subsequent TSP will require subsequent IPC insertion to manage recurrent MPE due to radiographically occult NEL.

The results of the recent IPC-PLUS study are likely to further increase the early use of IPCs once this evidence has been fully assimilated, externally validated

and incorporated into consensus guidance. However, it is important to recognise that the pleurodesis success rate reported in IPC-PLUS (51% at 10 weeks) [48] is significantly inferior to that documented in RCTs involving TSP (71 – 78%). This can be achieved after only a short initial admission (around 3-7 days) [3,5] obviating the need for indwelling prosthetic material, which is undesirable for many patients [43] Therefore, although IPCs are a critical and important therapeutic option for MPE management, they should not be considered a panacea for all patients.

In summary, a variety of interventions exist for the treatment of symptomatic MPE. These allow clinicians to tailor management to a significant degree based on expected prognosis and patient preferences, primarily based around TSP and IPC placement. However, radiographically occult NEL remains a persistent and unresolved confounder of truly precise deployment of these two strategies. This reflects current difficulties in the early and reliable detection of NEL, resulting in futile admissions for TSP and a resultant requirement for repeat pleural procedures. The particular methods by which NEL may be assessed in current clinical practice and in research settings are discussed further in the following section.

Table 1.4 Patient-centred considerations when choosing between IPC insertion and TSP as first-line interventions for symptomatic MPE

	Talc pleurodesis	**IPC insertion**	**Combination: IPC and ambulatory pleurodesis**
Advantages	Where successful, pleurodesis provides lasting control of symptoms without need for indwelling prosthetic material	May provide long term symptom control even where NEL present [4,46,47]	As per IPC Additionally, significantly increased chance of IPC removal (51% at 10 weeks) [48] over IPC alone
	Lower risk of infection compared with IPC use [39]	Can be inserted as a day case procedure [39]	
Disadvantages	Requires 3-7 day hospital admission [3,5]	Greater risk of infection compared with TSP over lifetime of IPC (5-10%) [2,42]	As per IPC IPC-PLUS trial suggests no increased risk associated with instilling talc slurry via IPC, Bhatnagar:2018ce} however pleurodesis success rates remain lower than expected with inpatient TSP
	Fails in around 30%, [5] often due to underlying NEL	Inconvenience of long-term indwelling prosthetic material and associated lifestyle restrictions e.g. unable to swim / bathe, uncomfortable in hot climates	

IPC, indwelling pleural catheter; TSP, talc pleurodesis; NEL, non-expansile lung

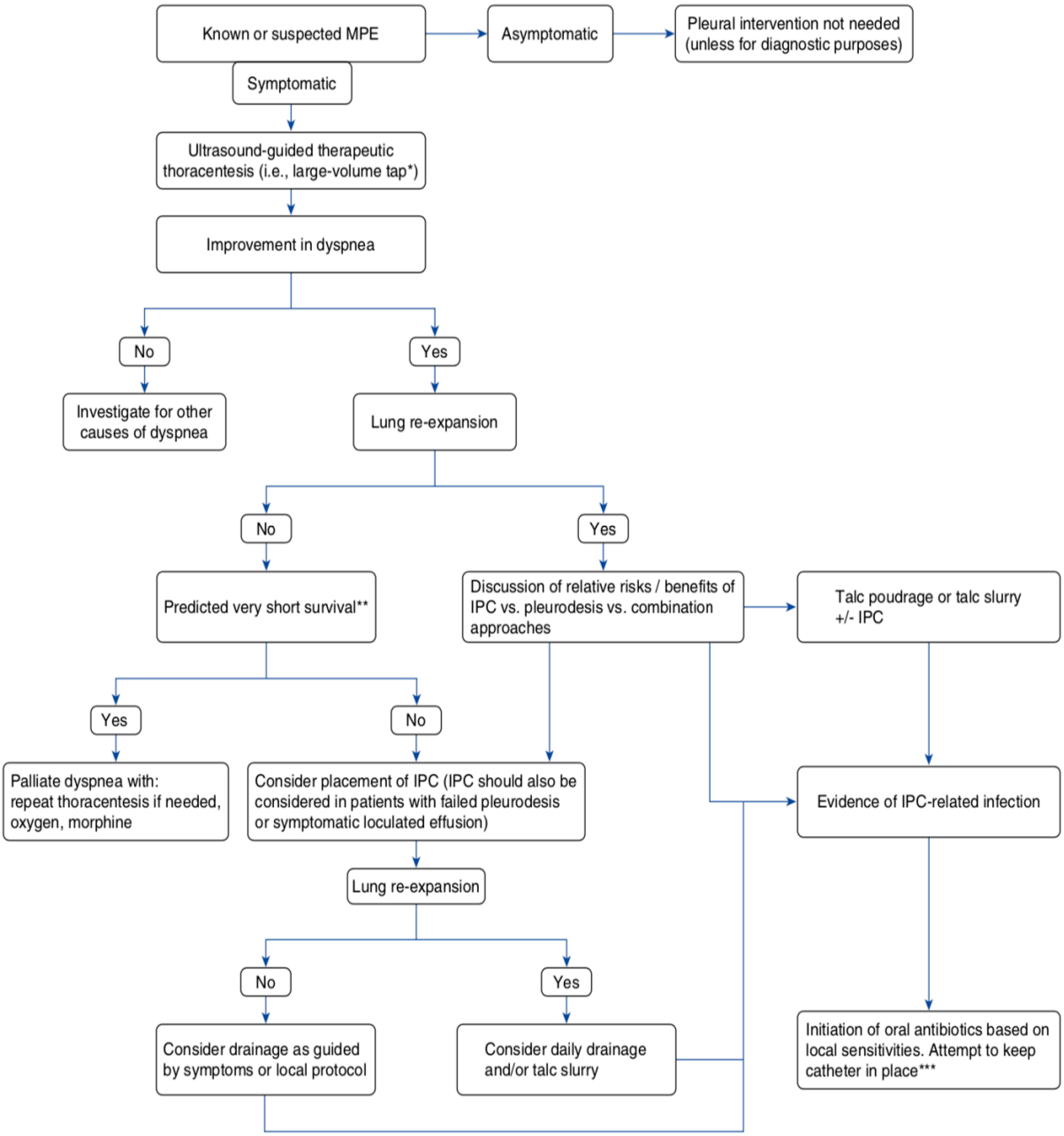
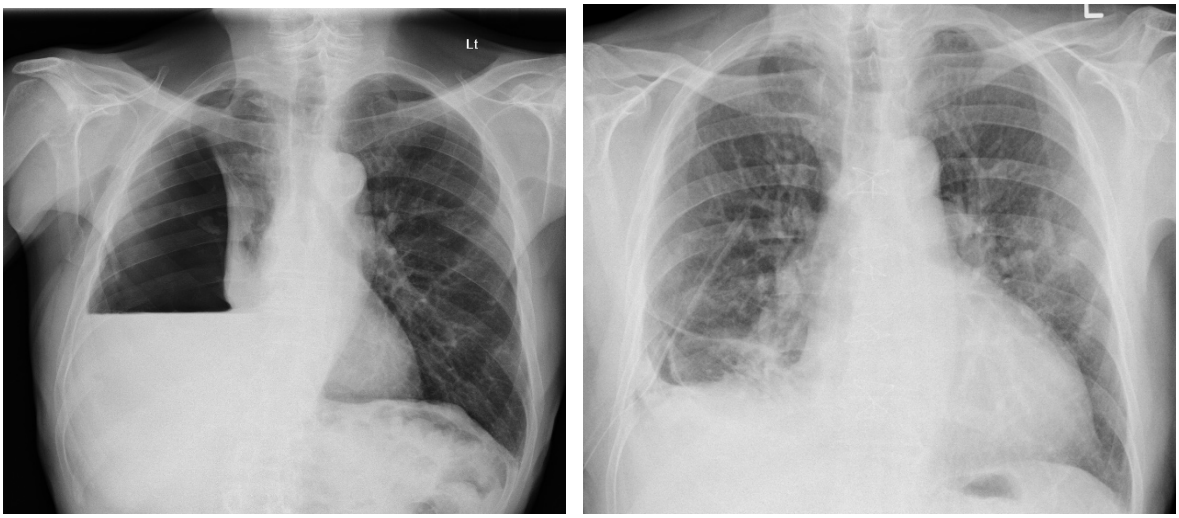


Figure 1.2 Flowchart of recommendations for the initial management of symptomatic known or suspected malignant pleural effusion (MPE) taken from American Thoracic Society 2018 guideline

1.5 Non-expansile lung in malignant pleural effusion

1.5.1 Nomenclature and pathophysiology

Non-expansile lung, also referred to as 'unexpandable lung', is an umbrella term to describe incomplete re-apposition of the visceral and parietal pleura following drainage of a pleural effusion of any aetiology. [49] It may occur as a result of pleural restriction, ipsilateral endobronchial obstruction, or chronic atelectasis. [50] In clinical practice a spectrum of lung re-expansion is encountered ranging from 'complete NEL' to lesser degrees of NEL as shown in Figure 1.3 below.



Panel A Panel B

Figure 1.3 Chest radiographs showing varying degrees of NEL following drainage of MPE. Panel A shows no evidence of lateral or basal pleural re-apposition consistent with 'complete NEL'. Panel B shows complete right upper lobe re-expansion but incomplete middle and lower lobe re-expansion consistent with a degree of partial NEL.

The terms 'trapped lung' and 'lung entrapment' are commonly used interchangeably to describe NEL. However, a different pathophysiological basis has been described in the literature. [49] The term trapped lung most accurately describes the situation in which there is an entirely fixed pleural cavity. This typically arises from defective healing of a pleural insult resulting in a constricting visceral peel. Over time, the initial active pleural inflammation may

resolve completely but the anatomical deficit is permanent. Classically, this results in an increasingly transudative pleural collection over time. [51] In contrast, entrapped lung describes the more common situation in which NEL is identified in the context of on-going active pleural inflammation that may potentially resolve without the development of permanent restriction. This distinction is particularly relevant in benign pleural disease such as parapneumonic effusion or haemothorax where prompt treatment with antibiotics and/or pleural drainage may prevent evolution to trapped lung. In the context of MPE however, the underlying mechanism and sub-type of NEL is relatively unimportant since all forms of significant NEL will render an attempt at inpatient TSP futile.

1.5.2 Radiological assessment of post-drainage non-expansile lung

1.5.2.1 Plain radiography

NEL is typically defined based on the appearance of a post-drainage CXR using subjectively estimated criteria describing the proportion of lateral pleural re-apposition. In a minority of cases, a pneumothorax (or hydro-pneumothorax) may be encountered. Historically, iatrogenic visceral pleural trauma was blamed for this finding, however point of care ultrasound guidance has reduced the rate of this complication from up to 18% [52] to around 1% when performed by an experienced operator. [53,54] This appearance is therefore most appropriately termed ‘pneumothorax ex-vacuo’ [4] and is thought to relate to transient parenychmal-pleural fistulae caused by pressure-dependent stress forces during aspiration when NEL is unable to conform to the shape of the thoracic cavity. [55]

An assessment of lung re-expansion may take place after partial drainage at the time of diagnostic thoracentesis, or after an attempt at complete drainage via ICD prior to planned talc slurry delivery. The degree of pleural re-apposition required for successful pleurodesis is unknown, although expert consensus suggests TSP may reasonably be attempted where at least half the visceral and parietal pleura are re-apposed on x-ray. [4] Although readily available, this approach is grossly insensitive for NEL detection, particularly following partial drainage where pneumothorax ex-vacuo is rarely encountered. To illustrate further, there is a clear discordance between estimated NEL prevalence in MPE

(13-32%), [35,48] and post-thoracentesis pneumothorax rates (18/799 (2.3%) patients who underwent aspiration of >1500ml in a large prospective cohort study). [54] This low sensitivity for NEL detection is also illustrated by experience from clinical trials. For example, in the IPC-PLUS and TAPPS trials a significant proportion of randomised patients (13% and 7% respectively) were excluded from trial interventions due to inadequate lung re-expansion, despite lung entrapment being an explicit exclusion criterion. [26,48] Post-thoracenetsis CXR appearances are therefore of limited utility in directing subsequent patient management.

1.5.2.2 Cross-sectional imaging

Use of 2-dimensional plain radiographs to estimate the total proportion of pleural re-apposition following pleural drainage is fundamentally limited since only the lateral position of the visceral pleura may be accurately delineated. Cross-sectional imaging using computed tomography (CT) or magnetic resonance imaging (MRI) allows a global assessment of pleural contact but are inherently unsuitable for bedside decision-making or immediate action in the OP clinic.

1.5.2.3 Thoracic ultrasound

The use of bedside thoracic ultrasound (TUS) is now ubiquitous in the practice of pleural medicine. [56] It is commonly employed to assess effusion size and guide decision making and site-selection for pleural procedures. There is also some evidence that post-drainage TUS appearances may predict subsequent TSP success. In a pilot study of 18 patients undergoing TSP by Corcoran *et al*, a systematic 9-point TUS was performed immediately before, and 1 day after, talc slurry instillation. [57] At each TUS site, lung sliding artefact was assessed and quantified as present (0), questionable (1) or absent (2) in order to calculate an overall pleural adherence score. Based on 15 subjects with adequate survival, a post-talc pleural adherence score of ≥ 10 predicted subsequent TSP success (radiological recurrence and requirement for repeat pleural intervention) at 1-month follow-up with a sensitivity of 82% at 92% specificity. [57]

Although not explicitly devised to detect or describe NEL, the multi-site TUS exam reported above may also have utility in predicting TSP success in cases with incomplete lung re-expansion. However, the generalisability of this approach may be limited since the sonographic appearances of pneumothorax

ex-vacuo may be readily confused with lung sliding by less experienced operators. The use of a pleural adherence score to direct the management of patients undergoing TSP (specifically the timing of talc instillation and timing of post-talc ICD removal) is now under prospective evaluation an in appropriately powered multicentre RCT (SIMPLE). [58] The results of this study are likely to significantly enhance our understanding of the utility of TUS in defining NEL following MPE drainage. This concept is also being explored in the OPTIMUM study, where a multimodal assessment (CXR, TUS and P_{EL}) of lung re-expansion following IPC drainage is undertaken prior to delivery of ambulatory intrapleural talc in patients with adequate pleural apposition. [59]

1.5.3 Prevalence of non-expansile lung

The true prevalence of NEL is difficult to ascertain since different definitions have been used in previous MPE studies, and the frequency of NEL is not reported at all in some. In most studies, NEL is defined based on post-drainage radiographic appearances. In the Phase III Intergroup RCT by Dresler *et al*, in which TSP and VATS talc poudrage were compared, NEL was defined as <90% lung expansion using subjective visual estimation of CXR appearances (TSP arm) or thoracoscopic appearances (VATS arm), and occurred in 30% of participants. [5] In a more recent observational MPE study of 70 patients with MPE (only 27% due to lung cancer), NEL was reported in 54% of patients using the same radiographic criterion. [60] In the AMPLE-2 trial, which compared alternative IPC drainage strategies, NEL was defined more grossly as air or fluid in the pleural space occupying 25% or more of the lateral chest wall after initial drainage. However, it was still a common finding, occurring in 32% of participants. [35]

The IPC-PLUS investigators reported additional details on the proportion of patients affected by NEL since differing degrees of lung re-expansion at different time points were used to a) determine eligibility for enrolment, b) minimise imbalance between the study arms, and c) determine eligibility for randomisation and completion of the trial interventions (i.e. instillation of talc slurry or placebo). In this trial, 41/923 screened patients (4%) were immediately excluded on the basis of obvious lung entrapment. Of 250 enrolled patients, 32 (13%) had “substantial” lung entrapment, defined as less than 75% pleural re-apposition on CXR, or more than one third pleural opacification due to fluid (based on thoracic ultrasound), following attempted pleural drainage. These

patients were excluded from randomisation. Of the 154 who were randomised, 30/154 (19%) subsequently had incomplete re-expansion (< 25% lung entrapment). [44]

1.5.4 Pre-drainage identification of underlying non-expansile lung

Detection of NEL prior to complete pleural drainage is challenging but highly desirable since this information could effectively be used to stratify the MPE pathway. In current practice, a subjective judgment on the likelihood of subsequent NEL is typically made by integrating pre-drainage CT predictors (e.g. overt proximal endobronchial obstruction, visceral pleural peel) and, where performed, the appearance of the visceral surface at LAT. However, such judgements are frequently inaccurate, prompting research interest in alternative pre-drainage markers of NEL such as M(motion)-mode and Speckle-tracking US and pleural manometry. The diagnostic performance of each technique is reviewed in the following sections.

1.5.4.1 CT appearances

Underlying NEL is often inferred from pre-drainage CT appearances where overt endobronchial obstruction or visceral pleural thickening are seen. The latter is not easily distinguished from pleural fluid or atelectatic lung unless air is intentionally introduced into the pleural space at the time of thoracentesis to provide 'air-contrast' imaging. [61] This technique has only been described in patients who developed symptoms consistent with NEL (chest discomfort and cough) during thoracentesis and therefore its safety and diagnostic performance in a generalised MPE population is unknown. To date, no studies have assessed the ability of pre-drainage CT to predict subsequent lung re-expansion or pleurodesis success.

1.5.4.2 Thoracoscopic appearances

A small proportion of patients with MPE undergo surgical thoracoscopy under general anaesthesia (GA). In this situation, the degree to which the affected lung can re-expand on removal of pleural fluid can be visually assessed. During GA surgical thoracoscopy, this is done by controlled application of positive pressure ventilation via a dual lumen endotracheal tube and direct visualisation by the surgeon. The most appropriate definitive management strategy (TSP vs. IPC) can then be implemented during the same procedure. In a series of 127

patients, Qureshi et al detected NEL in 52/127 cases using this technique, and reported an improvement in symptoms (after 2-weeks) in 49/52 cases (94%). [62] However, GA thoracoscopy carries additional risks and is unsuitable for the majority of patients with MPE, particularly those with poor performance status. The procedure also clearly requires referral to a tertiary thoracic surgery centre.

The visceral pleural surface can also be visualised during LAT in a spontaneously breathing patient. Although a single centres study reported by Ip *et al* reported modest success in predicting subsequent NEL (40/50 (80%) patients with NEL received an IPC; 34/53 (64%) patients with expandable lung received a ICD), this performance remains unacceptably error-prone. [63] In an earlier multi-centre survey based on video clips of LAT appearances, Hallifax *et al* reported even poorer performance with NEL correctly predicted in only 13% [64] These findings are consistent with unpublished audit data from the Glasgow Pleural Disease Unit which report correct identification of NEL at LAT in only 30% of patients [Personal communication: Prof Kevin Blyth, Glasgow Pleural Disease Unit].

1.5.4.3 Ultrasonography

As previously discussed, point of care TUS is a cornerstone in the practice of pleural medicine. Use of this imaging modality to non-invasively detect NEL prior to attempting MPE drainage is therefore an appealing proposition. An alternative approach to early NEL detection has been described by an Australian group using ultrasound characteristics of underlying atelectatic lung. [65] In this work, Salamonsen *et al* used m-mode and speckle tracking ultrasonography to assess lower lobe atelectatic lung motion and strain associated with cardiac impulse during a breath hold in 81 patients with suspected MPE. Using a subset of patients as a development cohort, the authors identified optimal cut-points for radiographic NEL detection of 1mm and 6% for m-mode and speckle tracking sonography, respectively. In the validation group, speckle tracking significantly outperformed m-mode sonography in the detection of NEL; sensitivity/specificity 50%/85% (m-mode) vs 71%/85% (speckle tracking) (95% CIs not reported). However, this study adopted a radiographic end point and therefore evidence of directly attributable patient benefit is lacking. Doubt also remains over the generalisability of these methods, particularly regarding strain assessment using speckle tracking which requires specialist equipment and training. Figure 1.4 shows an example of m-mode TUS image acquisition.

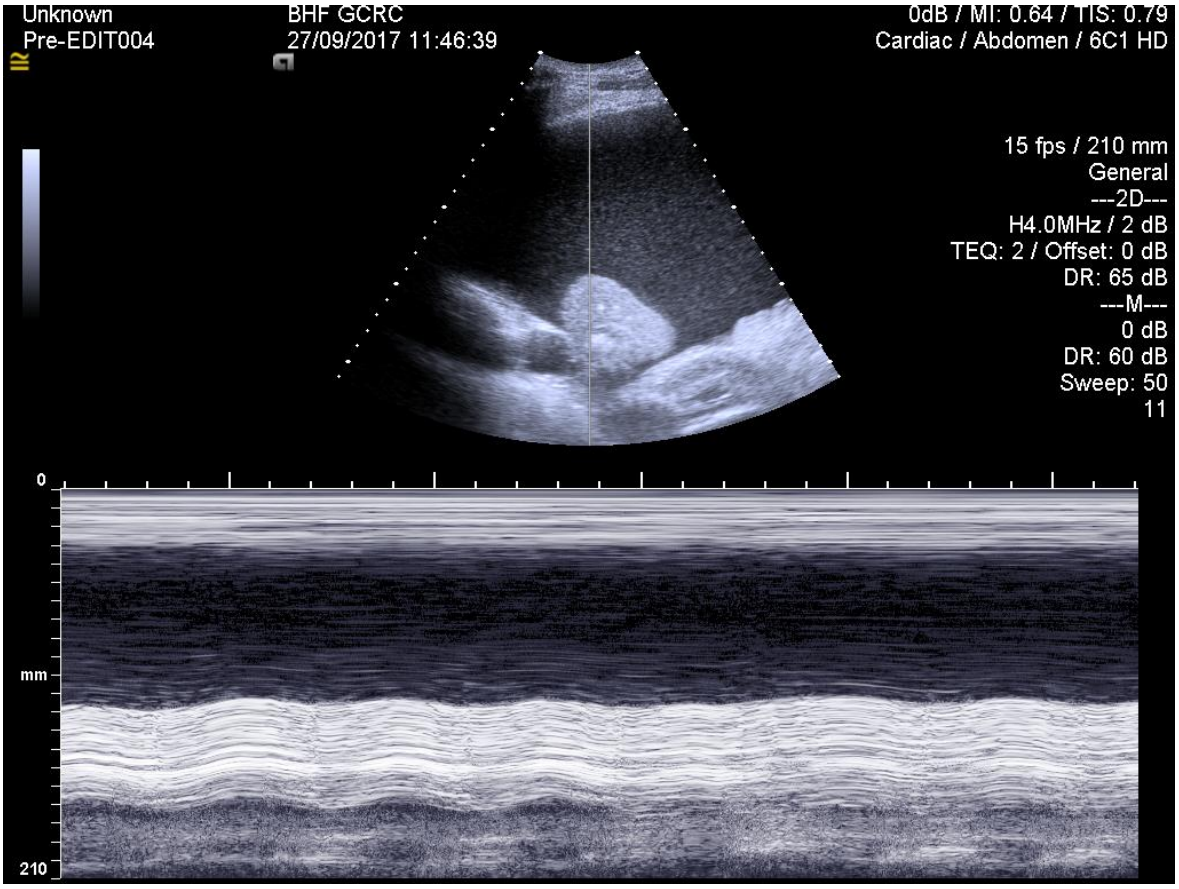


Figure 1.4 TUS image in a pre-EDIT trial subject with MPE showing m-mode data acquired from a region of interest placed over the underlying atelectatic lung during a breath hold

1.5.4.4 Pleural Manometry

Pleural elastance (P_{EL}) an intrinsic property of the pleural space. It is defined as the change in intra-pleural pressure (IPP) per unit volume of pleural fluid removed ($\Delta IPP/\Delta V_{OUT}$) and can therefore be readily calculated from data obtained during thoracentesis if concurrent IPP measurements are taken. [66] Abnormally high P_{EL} has previously been associated with the subsequent radiographic finding of NEL. [67] However, P_{EL} assessment has not matured into routine practice due to both technical challenges that make reliable IPP measurement difficult and a lack of evidence that manometry use directly improves patient outcomes.

Over the preceding 6 years, we have collaborated with a commercial partner (Rocket Medical UK (Washington, UK)) to develop of a novel. custom-built digital

pleural manometer (DPM) that specifically addresses many of the technical issues encountered in the past. This provided a unique opportunity to robustly reassess the clinical utility of pleural manometry in MPE management. In the following section, I review the evolution of pleural manometry, including the technical limitations previously encountered and the new DPM that was evaluated and reported in this thesis.

1.6 Pleural manometry

1.6.1 Development of pleural manometry

Pleural manometry is not a new technique; measurement of IPP during fluid aspiration was originally described in the 19th century and found clinical utility in the guidance of pneumothorax induction for the treatment of pulmonary tuberculosis in the pre-chemotherapy era. [68] Interest in the clinical utility of pleural pressure measurements returned in the 1980s as a potential adjunct to therapeutic pleural aspiration – primarily with safety in mind during large volume aspiration. [66] In a seminal study by Light *et al*, 52 patients had IPP measurements taken intermittently (at 200ml intervals) using an analogue (U-shaped) water manometer during large volume aspiration. Although the data from this study proved to be of limited diagnostic value for NEL, this report proved the technical feasibility of measurement acquisition, prompting development of improving apparatus and the growth of a pleural manometry research community.

1.6.2 Pleural manometry: technical considerations

1.6.2.1 Water column manometry

Simple water column manometers were first used to perform pleural manometry. Although cheap, it is challenging for the operator to obtain accurate pressure readings with these devices due to oscillation of the column during the respiratory cycle. Damping of the water column using a fine bore needle (22 gauge) has been described to mitigate this, but increases the complexity and inconvenience of the procedure. [69] The requirement for manual recording of data is a further disadvantage to this analogue technique.

1.6.2.2 Electronic transduction

Improvised electronic systems using haemodynamic transducers, originally intended for central venous pressure monitoring, were the next evolution but added further complexity to the procedural set-up. Sterility of the aseptic field may also be compromised by the need to for external wiring to link the transducer to its display and data recording remains burdensome as display units are not configured to present serial IPP measurements. Within the last 8 years, a commercially available single-use disposable digital manometer (Compass;

Mirador Biomedical, Williamston, USA) has been developed. While adding cost, this device simplifies electronic measurement of IPP and has been validated against water column and improvised electronic systems. [70] However, the Compass system remains confounded by poor pressure-damping resulting in rapid oscillations that make pressure recording at any given timepoint challenging.

1.6.2.3 Continuous intra-pleural pressure measurement

The methods described thus far in this thesis limit the operator to intermittent IPP measurement. This limitation exists because pressure is measured from the column of water within the main lumen of the aspiration equipment. Externally stimulated flow (e.g pleural fluid aspiraton) through a water column manometer, or in proximity to an electronic transducer, will thus confound data recordings. For example, significant negative IPP may arise in the unmonitored period whilst each aliquot of fluid is removed. A proof-of-concept study to overcome this limitation describes continuous IPP recording using an epidural catheter, linked to an electronic transducer, within the lumen of an intercostal chest drain. This apparatus was connected to urodynamics equipment and allowed real-time $\Delta IPP/\Delta V_{OUT}$ data, and therefore P_{EL}, to be plotted for the first time. [65] However, such a complex improvised arrangement is clearly impractical for widespread routine clinical use, prompting development of the bespoke, dual lumen manometry catheter with our commercial collaborators, Rocket Medical UK (Washington, UK).

1.6.3 Rocket Medical (UK) digital pleural manometer

The Rocket digital pleural manometry (DPM) catheter is shown in Figure 1.5. It is the first custom-built and fully integrated system specifically designed for pleural manometry during pleural aspiration. It is based on an existing commercially available 8Fr pleural aspiration catheter with verres safety needle to minimise the risk of visceral injury during insertion. An additional external “cuff” surrounds the base of the catheter. This incorporates a narrow second lumen allowing the electronic transducer to communicate with the pleural cavity independently of the fluid drainage channel and record spatially damped IPP once per second. During use, this disposable catheter is connected to a re-usable display unit which displays real-time IPP data as a rolling average of the

recorded IPP data over the preceding 5 seconds. Visual and audible warnings are given as increasingly negative IPP is reached.

Figure 1.5 Rocket DPM catheter and display unit

1.6.4 Patterns of intra-pleural pressure change during thoracentesis and implication for diagnostic criteria for NEL

Observational studies prior to development of the Rocket DPM have allowed recognition of three patterns of IPP change during fluid removal, which appear to correlate with distant biomechanical phenotypes ('expandable', 'entrapped' and 'trapped', see Figure 1.6 overleaf). [66,69,71,72] On this figure, Curve A represents normal pleural physiology and is associated with expandable lung. By contrast, Curves B, C and D all demonstrate an abnormally rapid fall in IPP during aspiration which is associated with NEL. In curves C and D, there is an early and rapid fall in IPP as fluid is removed. This pattern of pressure change is pathognomonic of the trapped lung sub-group of NEL in which there is a fixed pleural cavity. In contrast, curve B initially mirrors the behaviour of expansile lung until an inflection point is reached, beyond which the pleural cavity can no longer accommodate to volume of fluid removed. This pattern is seen in lung entrapment and reflects initial lung re-expansion.

In the design of diagnostic criteria for NEL based on manometry data it is clearly of critical importance that curve patterns B, C and D can all be detected. This is because all are three biomechanical phenotypes are likely to result in TSP failure. The logical conclusion for this data is that optimal sensitivity for NEL will require a large volume of fluid to be aspirated. In some patients with subtle degrees of NEL, it might ultimately maximise sensitivity to perform a near-complete effusion aspiration procedure. However, current BTS guidelines, recommend that therapeutic aspiration is limited to 1.5L in a single procedure. [4]. This volume limit may preclude detection of all cases of biphasic NEL, and I hypothesise that for P_{EL} assessment to be developed into a useful NEL biomarker larger aspiration volumes will be needed. This will be explored in Chapter 4 in the prospective pre-EDIT clinical trial.

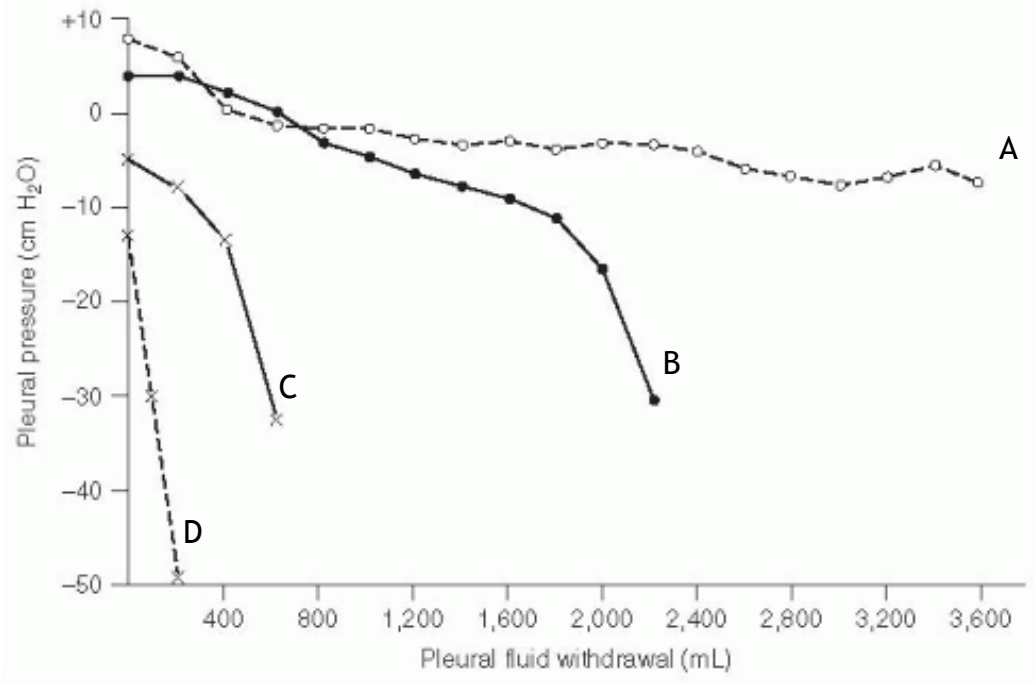


Figure 1.6 Sequential intra-pleural pressure measurements in 4 subjects during thoracentesis plotted against aspiration volume to produce 'pleural elastance curves'. Curve A represents normal pleural physiology associated with expandable lung. Curve B demonstrates 'biphasic' physiology associated with NEL. Curves C and D demonstrate 'trapped lung' which is a sub-group of NEL.

1.6.5 Risk associated with measurement of pleural elastance during a larger volume aspiration

Current advice limiting therapeutic aspiration to 1.5L is based on the risk of iatrogenic pneumothorax or re-expansion pulmonary oedema (RPO). Of these events, RPO is the more significant, having a reported mortality rate of up to 20%. [73] However, a recently published prospective series of 9320 procedures (performed without pleural manometry) confirm a low absolute risk of RPO but progressive probability of precipitating RPO as larger fluid volumes are removed. An incidence of 4/8486 (0.05%) was reported where 1-1500ml were aspirated compared with 6/799 (0.75%) for volumes greater than 1500ml ($p<0.0001$). [54]

The exact pathophysiology of RPO is not fully understood but evidence from animal models shows an association between increasingly negative IPP and the development of pulmonary oedema. In one study, rabbits with pneumothorax were exposed to an IPP of -20 mmHg (approximately -27 cm H_2O) with minimal risk of pulmonary oedema compared with a significant risk when a pressure of -40mmHg (approximately -54 cm H_2O) was applied. [74] This led Light *et al*, somewhat arbitrarily, to choose -20 cm H_2O as a cut-off point to terminate therapeutic thoracentesis in their seminal manometry work in which none of the 52 participants developed RPO despite aspiration volumes of up to 3400ml. [66] In a larger series using the same IPP threshold, Feller-Kopman *et al* identified only one case of clinically apparent RPO in 185 patients undergoing therapeutic thoracentesis with a mean aspiration volume of 1670ml (range 1 - 6.5L, SD 760ml). [75]

In contrast to RPO, it was initially thought that iatrogenic pneumothorax was not prevented by IPP monitoring. In an observational cohort study of 192 subjects undergoing large volume thoracentesis with concurrent pleural manometry, 8 developed an unintentional pneumothorax of which only 4 had evidence of abnormal P_{EL}. [55] However, a subsequent RCT involving 124 participants who underwent therapeutic thoracentesis, with or without additional manometry-directed stop criteria, identified only 6 cases of pneumothorax ex-vacuo, none of which were in the manometry arm ($p=0.012$). [76]

The consequences of pneumothorax in this situation also appear far less severe than RPO; they are typically asymptomatic and do not require further intervention. [76] These data support the use of larger aspiration volumes to enhance the diagnostic potential of P_{EL} in the detection of NEL.

1.6.6 Development of chest discomfort during pleural aspiration and relationship to pleural manometry

A relationship between negative IPP and chest discomfort during thoracentesis has previously been reported. [61,77] In an observational study of 169 patients by Feller-Kopman *et al*, the mean IPP measured at the end of thoracentesis was -6.7 cm H_2O in those without discomfort vs -13 cm H_2O for those with discomfort (p=0.04). [77] Additionally, the mean change in IPP for those without discomfort was -12.4 cm H_2O vs -20 cm H_2O for those with discomfort (p=0.001). There was also a trend towards higher P_{EL} in patients who experienced chest discomfort, but this association did not reach statistical significance. [77] These findings were supported by another observational study in which it was noted that in patients with post-thoracentesis discomfort, the iatrogenic reintroduction of intrapleural air, which was assumed to thereby increase IPP, frequently led to immediate relief of symptoms. [61] The authors termed this intervention 'therapeutic pneumothorax'.

However, previous studies also identify important inconsistencies between negative IPP and the occurrence of chest discomfort. In their study, Feller-Kopman *et al* identified a number of discordant findings; e.g. only 4/18 (22%) who experienced discomfort had excessively negative IPP, and 12/140 (9%) without symptoms had IPP < -20cm H_2O. [77] These findings suggest that individual tolerance of negative IPP varies widely and it has been hypothesized that this may, in part, relate to regional variations in P_{EL} and therefore variability in areas of visceral pleural stress. [55]

The hypothesis that avoidance of excessively negative IPP during thoracentesis might reduce the likelihood of chest discomfort developing was prospectively tested in a rigorously conducted single-blind RCT recently reported by Lentz *et al*. [76] In this study, patients with symptomatic MPE were randomised to either a standard symptom-guided thoracentesis (terminated if chest discomfort or intractable cough developed) or a symptoms *plus* manometry-directed

thoracentesis (terminated by symptoms, or end-expiratory IPP ≤ –20 cm H_2O, or IPP declined by more than 10 cm H_2O between two measurements to a value less than or equal to –10 cm H_2O). No difference in chest pain scores from the start of the procedure to 5 minutes post-procedure were seen between the groups. The previously described individual variation in negative IPP tolerance may account for this negative result. Another explanation proposed by the authors is that the use of intermittent IPP (using the in-line Compass system described in Section 1.6.2.2) rather than continuous IPP monitoring may have limited the ability of pleural manometry to detect significant falls in IPP prior to transient pleuro-parenchymal fistulation occurring. Nevertheless, this important negative study does not support use of intermittent IPP monitoring using the Compass system as a means of reducing chest discomfort. However Lentz *et al* do acknowledge that manometry may still have utility in the detection of NEL and the prediction of pleurodesis success, since these questions were not addressed in their study.

1.6.7 Pleural elastance as a predictive biomarker of non-expansile lung

To date, only one study has sought to prospectively evaluate the predictive value of P_{EL} for the presence of NEL and subsequent pleurodesis success. Lan and colleagues found that $P_{EL} \geq 19$ cm H_2O/L measured during the initial 500ml of a therapeutic thoracentesis predicted NEL with a moderate sensitivity of 79% at 94% specificity. Using the same cut-off, there were no patients with an elevated P_{EL} who had successful pleurodesis compared with 98% success in the lower P_{EL} group. [67] The relatively small aspiration volume used in this study to calculate P_{EL} is probably the principle explanation that sensitivity for NEL was only 79%. Aspiration of only 500 ml fluid is unlikely to identify biphasic biomechanics due to entrapped lung (as discussed earlier in Section 1.6.4).

Subsequent to the Lan *et al* study, the upper limit of normal P_{EL} was established as 14.5 cm H_2O/L, based on theoretical modelling and subsequent clinical validation in a series of 192 patients. [55] Using this lower cut-point, Chopra *et al* recently identified abnormal P_{EL} in 36/70 (51%) patients undergoing large volume thoracentesis for MPE. [60] In this cohort, abnormal P_{EL} was strongly associated with radiographic NEL (defined here as <90% expansion), although a number of discordant results were observed, which translate again into

insufficient sensitivity and specificity. 9/36 (25%) patients in this study who had abnormal P_{EL} were considered false positives (low specificity) since they demonstrated complete lung re-expansion, while 11/34 (32%) patients with normal P_{EL} were false negatives (low sensitivity) since they had subsequent radiographic NEL.

Probable reasons for this poor performance include use of the in-line Compass system which only allows intermittent IPP recording and is poorly damped, making consistent recording at any single timepoint difficult. Other possibilities include loss of specificity due to the lower P_{EL} cut-point used (≥14.5 cm H_2O/L), or transient drops in IPP due to incomplete expansion that then resolves (likely subsegmental areas of atelectasis that take more than a few seconds to open up). Loss of sensitivity may have reflected early termination of the procedure for other reasons, e.g. chest pain due to pleural irritation from the catheter tip, or transient pressure dependent pleural-parenchymal fistulation may have led to paradoxical normalisation of P_{EL}. The development of P_{EL} into a clinical useful biomarker for NEL must learn from these data, and should also relate P_{EL} values to patient-centred, rather than radiographic, end points.

1.7 Validation of the definition of pleural elastance

As described earlier, P_{EL} is an intrinsic property of the pleural space, but it is defined as the change in intra-pleural pressure (IPP) per unit volume of pleural fluid removed ($\Delta IPP/V_{OUT}$). This definition therefore incorporates an assumption that the volume of pleural fluid removed is exactly equal to the volumetric change of the pleural space. However, this assumption and thereby the current definition of P_{EL} have never been objectively validated.

This is particularly important, since as already outlined, ΔIPP correlates with the development of chest discomfort, but P_{EL} does not, [77] the assumption that the volume of fluid removed accurately represents the internal change in volume of the pleural cavity may be incorrect. Variable compliance of the lung, chest wall and diaphragm, and the potential for introduction of liquids (local anaesthetic, pleural fluid or blood) and air, either through instrumentation or clinically occult transient parenchymal-pleural fistulae, may account for this discrepancy.

Pre- and post-thoracentesis volumetric MRI would provide gold standard measurements of internal pleural cavity volume change (ΔV_{MRI}) without undue risk or inconvenience to study participants. This approach is supported by the experience from the recently completed DIAPHRAGM multicentre blood biomarker study, in which a well-tolerated pleural MRI sub-study was undertaken in a range of patients with varying sizes of pleural effusion. [78] ΔV_{MRI} data can then be compared to corresponding aspiration volumes (V_{OUT}) to assess the level of agreement, and in turn, the validity of the conventional definition of P_{EL}. Basic MRI theory is briefly reviewed in the sections below, followed by a summary of the evidence supporting the use of this technique as a gold standard for intrathoracic volume assessment.

1.7.1 Basic MRI theory

1.7.1.1 Nuclear magnetic resonance

Magnetic resonance imaging (MRI) utilises the nuclear magnetic properties of Hydrogen atoms within body tissues when exposed to magnetic fields of varying field strengths. Hydrogen atoms are abundant in body tissues (particularly fluids and adipose compartments) and comprise a central nucleus formed from a single proton, orbited by a single electron. However, for the purposes of MRI the

electron is considered redundant and the proton the focus of attention. All protons possess an inherent quantum property known as ‘spin’ which generates a magnetic field around each proton. The orientation of each protons’ spin axis is random. However, if a strong magnetic field is applied (termed B_0), protons align with the direction of B_0, either in a stable parallel (low energy) state, or an unstable anti-parallel (high energy) state. In addition, the protons ‘precess’ which means that their spin vector rotates around the direction of B_0. The angular frequency of their precession (termed the Larmour frequency) is determined by the magnetic field strength and the gyromagnetic ratio, a constant for any given nucleus (42.57 MHz/Tesla for a single proton). Since the majority of protons align parallel to B_0, the sum of each proton’s magnetic field forms a net longitudinal magnetisation in the direction of B_0.

1.7.1.2 Radiofrequency excitation

During MRI scanning, an excitatory radiofrequency (RF) pulse is applied to the body. The protons with the same precessional frequency as the RF pulse frequency ‘flip’ into a higher energy state and, importantly, start to precess in phase with each other. The net effect is that the sum of the nuclear magnetic spins rotates into the transverse plane and is thus detectable since it is no longer dwarfed by the strong B_0 longitudinal field. The degree to which the net magnetisation rotates is termed the flip angle and determined by the amplitude and duration of the RF pulse.

1.7.1.3 Relaxation

When the RF pulse is removed, protons lose the energy previously absorbed and relax into their original state. In doing so, RF energy is released which is detectable by receiver coils placed around the scanning subject. The detected returning RF pulse is termed a magnetic resonance (MR) signal.

There are two independent forms of proton relaxation; T1, the recovery of longitudinal net magnetisation, and T2, the decay of transverse magnetisation due to the loss of in-phase precession. The rate of T1 and T2 relaxation of individual protons varies depending on the composition of the tissue in which they are located and is an important determinate of tissue contrast. MRI scanners can be manipulated to produce images weighted towards T1 or T2 contrast.

1.7.1.4 Construction and appearance of magnetic resonance images

In addition to a main electromagnet (to generate B_0), MRI scanners contain weaker gradient coils which augment B_0 and create a graded magnetic field in axial, coronal and sagittal planes. By creating a graded longitudinal magnetic field during the excitatory RF pulse, MR signals may be isolated to an individual slice in which the proton precessional frequency is known to match that of the RF pulse applied. This is termed a 'slice encoding gradient'. Additional 'frequency encoding' and 'phase encoding' gradients applied during MR signal measurement allow three-dimensional localisation of the MR signals. The raw analogue MR signals are digitised and deposited into 'K-space' prior to the construction of an MR image which takes place via a computer process known as Fourier Transformation.

In the final MR images, areas of free water (e.g. pleural fluid) appear dark on T1-weighted images (see Figure 1.7) in contrast to fat which has a fast T1 relaxation and therefore appears bright. From a pleural perspective, T1-weighted images are therefore considered ideal for delineating anatomy and demonstrate excellent contrast between abnormalities in the pleural space and extrapleural fat. [79] On T2-weighted imaging, free fluid appears bright in contrast to lung and muscle (see Figure 1.8). T2 images therefore clearly highlight pleural fluid and delineate tumour from muscle. [79]

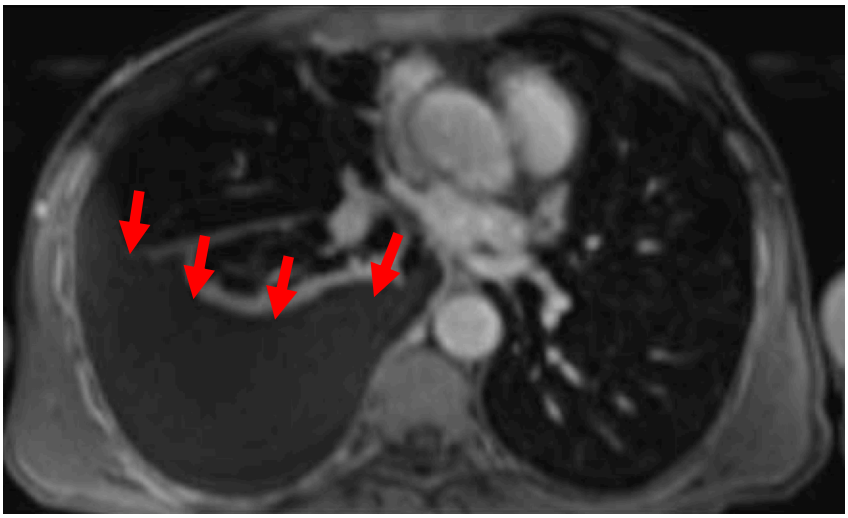


Figure 1.7 T1-weighted axial image of a patient with a right pleural effusion (indicated by arrows), taken post-contrast using a 3T Siemens Magnetom PRISMA® MR scanner at the Glasgow Clinical Research Imaging Facility, QEUH

Reproduced with the permission of Dr Selina Tsim.

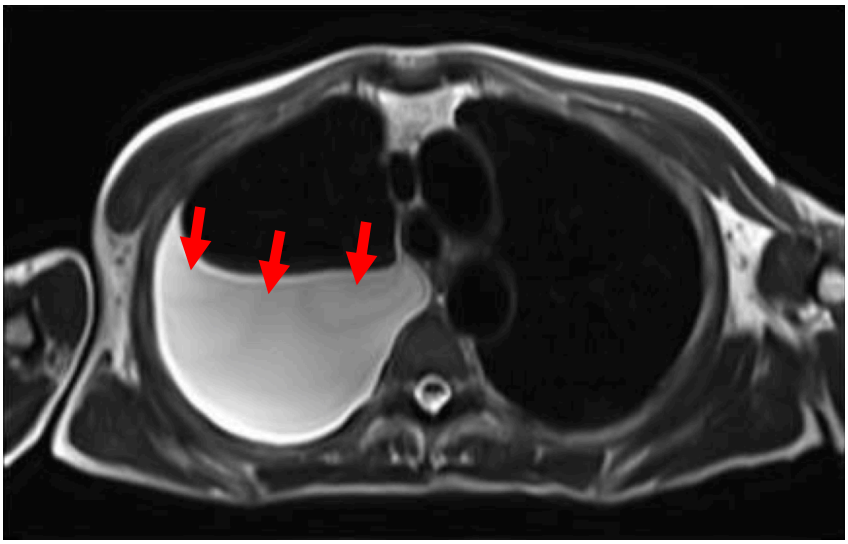


Figure 1.8 T2-weighted axial image of a patient with a right pleural effusion (indicated by arrows), taken pre-contrast using a 3T Siemens Magnetom PRISMA® MR scanner at the Glasgow Clinical Research Imaging Facility, QEUH

Reproduced with the permission of Dr Selina Tsim.

1.7.2 Magnetic resonance imaging: a volumetric gold standard

MRI is a well-established technique for the non-invasive volumetric assessment of intrathoracic structures. Cardiac MRI (CMR) volumetry in particular has been extensively studied. For example, left ventricular (LV) volume measurement has been validated against calibrated ventricular angiography (an historical gold standard technique), [80] and subsequently shown a high degree of inter-observer agreement. [81] Further *ex vivo* validation of CMR LV volume assessment has also been undertaken using a canine model; in a study involving 12 explanted hearts, the authors report a very strong correlation between *ex vivo* and CMR LV volumes ($r^2 = 0.98$), although data on agreement was not reported. [82] Nonetheless, CMR volume assessment has been shown to demonstrate an exceptionally high level of interstudy reproducibility and is widely regarded as the gold standard non-invasive technique for this purpose. [83]

A number of comparisons may be drawn between the internal volume of the cardiac ventricles and the pleural cavity; both are fluid-filled free-flowing intrathoracic structures and subject to similar imaging artefacts and challenges. It is therefore reasonable to assume that MRI represents an appropriate reference standard against which to assess the definition of P_{EL}, as previously discussed.

1.8 Evidence Synthesis and Design of an optimised treatment pathway

1.8.1 Importance of NEL recognition

As discussed, NEL is a common complication of MPE management. Future routine use of first-line IPC insertion either with, or without, ambulatory TSP may overcome many of the limitations of treatment with TSP but commits all patients to indwelling prosthetic material with its associated risks and inconvenience. Early detection of NEL would facilitate patient choice of initial management strategy (IPC vs TSP) for those with expansile lung and, importantly, protect those with NEL from futile attempts at TSP. It therefore logically follows that an optimal MPE treatment pathway should aspire to include an early assessment of lung re-expansion potential.

1.8.2 Choice of NEL biomarker

Existing clinical techniques (CT, LAT and CXR appearances following initial diagnostic thoracentesis) are insensitive in the pre-drainage detection of NEL. While TUS techniques show promise, there is a greater body of evidence to support the further development of peak P_{EL} as a NEL biomarker. Additionally, the recent technical advances in pleural manometry equipment (Rocket Medical (UK) DPM) further enhance the potential widespread and rapid uptake of this technique if shown to be of benefit to patients. This decision is justified further in Section 4.1.3 (page 132).

1.8.3 Choice of pleural elastance threshold

The peak P_{EL} threshold of 19 cm H_2O/L adopted by Lan et al achieved 79% sensitivity for NEL detection over a 500ml aspiration volume. A higher sensitivity would clearly be desirable in an elastance-directed pathway to minimise TSP failure. As described in Section 1.6.7, a larger aspiration volume may facilitate detection of additional cases of biphasic NEL. However the consequences of a near maximal drainage of fluid may then compromise the operator's ability to immediately place either an ICD or IPC since there may not be sufficient residual pleural fluid for Seldinger drain insertion. In Chapter 4, I will report on use of a abnormal P_{EL} threshold over the course of a near maximal drainage, but will use TUS to ensure that sufficient volume of fluid remains to allow immediate tube placement. In addition, I will adopt a lower P_{EL} threshold than Lan *et al*, in order

to increase the sensitivity of the procedure to detect NEL. Since the upper limit of normal P_{EL} has now been established at 14.5 cm H_2O/L, [55] this is a more logical cut-point to explore in the pre-EDIT trial. Any reduction in P_{EL} threshold will inevitably compromise specificity for NEL detection, however I will seek to mitigate any potential loss of specificity by use of a rolling average of P_{EL} during aspiration. This will avoid misclassification of cases as NEL due to transient falls in IPP that may arise as a result of temporary incomplete expansion, for example as a result of sub-segmental areas of atelectasis which require a short period of time to release. Use of a rolling average would theoretically also allow detection of abnormal physiology in biphasic cases at the earliest opportunity thereby minimising the aspiration volume required, and in turn, increasing the safety and technical ease of subsequent pleural access. This novel choice of NEL biomarker is discussed further in Section 4.1.5 (page 133).

1.8.4 Evaluation of MPE treatment success

Historically, radiographic endpoints have been used to define MPE treatment 'success', often with poor correlation to patient reported symptoms and unknown inter-observer reliability. Latterly however, the adoption of more clinically relevant patient-centred end points has resulted in better quality evidence on which treatment decisions may be based. [9] Standardised MPE intervention trial end points have not been formally established, although the majority of recent high quality studies in the field have used the requirement for repeat pleural intervention (typically at 3 months), Visual Assessment (VA) scores, or duration of hospitalisation, as clinically relevant means of defining treatment success. [2,27,84] Quality of Life (QoL) scores are also often recorded as unpowered secondary or exploratory endpoints.

1.9 Overall aim and hypothesis of this thesis

The overarching aim of the work presented in this thesis was to refine the management of patients with symptomatic MPE through improvements in NEL detection. The central hypothesis was that NEL was clinically important and that precise detection of NEL will enhance clinical outcomes by allowing more rational deployment of inpatient TSP and outpatient IPC insertion. This hypothesis has been addressed through:

- A retrospective multicentre MPE cohort study to determine the prevalence of NEL, the reproducibility of different radiographic definitions of NEL and any prognostic significance of these findings.

- A prospective assessment of the feasibility of a RCT testing a novel, P_{EL}-directed MPE treatment pathway called EDIT (**E**lastance-**d**irected **I**PC or **T**SP).

The materials and methods for these studies are detailed in Chapter 2. The results are presented and discussed in three individual results chapters. The individual hypotheses for each results chapter are summarised below.

1.9.1 Chapter 3: 'Post-drainage radiographic identification of non-expansile lung and its prognostic significance'

NEL is currently defined arbitrarily on the basis of subjective visual assessment of pleural re-apposition on post-drainage CXRs leading to significant variability in clinical decision making. Additionally, the clinical significance of NEL in terms of prevalence and potential prognostic impact are uncertain. These data are important in the rational design and conduct of future clinical research. The hypotheses of this chapter were:

- NEL is common and is under-represented in important previous MPE intervention studies.

- Greater objectivity in the radiological definition of post-drainage NEL would improve inter-observer agreement in post-drainage NEL detection and therefore the consistency of clinical decision making within existing MPE treatment pathways.

- NEL may have an association with survival and therefore contribute to prognostic scoring systems for clinical use and minimisation of imbalance between study groups in RCTs.

1.9.2 Chapter 4: 'Feasibility of a pleural elastance directed malignant pleural effusion treatment pathway'

Assessment of P_{EL} has shown potential as a pre-drainage biomarker of NEL. This chapter describes the feasibility results of the pre-EDIT study; an RCT of an elastance-directed treatment pathway (EDIT; **E**lastance-**d**irected **I**PC or **T**SP) for MPE in which definitive pleural management was stratified per protocol by a prediction of lung re-expansion potential. The hypotheses of this chapter were:

- EDIT management is technically feasible and safe to deliver.
- It is feasible to recruit sufficient numbers of patient to a future RCT testing the efficacy of a P_{EL}-directed MPE treatment pathway based on a patient-centred primary outcome measure.

1.9.3 Chapter 5: 'Optimisation of an elastance-directed management pathway for malignant pleural effusion'

The pre-EDIT study provided an invaluable opportunity to test assumptions regarding the current definition of P_{EL} and elements of the potential future EDIT trial design. The hypotheses tested in this chapter were:

- An initial TUS estimate of pleural effusion volume can be used to reliably calculate an aspiration volume that leaves a residual effusion large enough for safe Seldinger drain insertion at the same sitting (where residual effusion volume is arbitrarily set at 500ml)
- Pleural aspiration volume during thoracentesis (V_{OUT}) is equal to the pleural cavity volume change, and thus the current definition of P_{EL}, is accurate
- An aspiration volume greater than 500ml (which was used in previous studies) is required to detect all cases of NEL using P_{EL} (including those exhibiting biphasic biomechanical physiology)

- Patients with symptomatic MPE consider inpatient TSP a valuable first-line definitive intervention, and it is not the case that all are willing to undergo outpatient IPC management.

- P_{EL} is a superior biomarker for detection of NEL than M-mode sonography.

Chapter 2

MATERIALS AND METHODS

2 Chapter 2: Materials and Methods

2.1 Overview

The aims of this thesis have been addressed through two discrete pieces of clinical research. First, a two-stage retrospective analysis of patients with pleural effusion drained at LAT, and second, a feasibility RCT that evaluated a novel elastance-directed MPE management pathway (the pre-EDIT study). This chapter describes the design and data collection for these studies. The Chief Investigator for both studies was Prof Kevin Blyth, Queen Elizabeth University Hospital, Glasgow, UK.

2.1.1 Retrospective LAT analysis

This retrospective work was performed in two stages. In the first stage, two novel definitions of post-drainage radiographic NEL were evaluated in a single-centre cohort study of patients undergoing LAT. A univariate analysis testing the association between NEL and subsequent survival in this first cohort was also undertaken and proved positive. In the second stage, data regarding a larger cohort of LAT patients was therefore was collected to facilitate a multivariable analysis testing the relative importance and independence of the apparent prognostic impact of post-LAT NEL. The external validity of these findings were then assessed in an independent cohort from another UK centre.

2.1.2 Pre-EDIT study

Pre-EDIT was designed to assess the feasibility of a future phase III trial evaluating the efficacy of a novel, P_{EL} directed MPE treatment pathway (**E**lastance-**D**irected **I**ndwelling pleural catheter or **T**alc slurry pleurodesis; EDIT management). In pre-EDIT, patients were randomised to either first-line TSP (control group) or EDIT management, allowing both technical feasibility and recruitment feasibility to be assessed. Pre-EDIT also provided an invaluable opportunity to refine technical aspects of the proposed EDIT pathway and trial design.

2.2 Post-drainage radiographic identification of Non-expansile Lung and its prognostic impact – Stage 1

A single-centre retrospective cohort study was performed at the Queen Elizabeth University Hospital, Glasgow (QEUH). The study was sponsored by NHS Greater Glasgow and Clyde. Study activities were approved by the South Central - Hampshire B Research Ethics Committee (Ref: 17/SC/0351). This allowed use of unconsented linked anonymised data by clinicians directly involved in the patients' care.

2.2.1 Patient selection

This stage of the study included consecutive patients who underwent complete drainage of a pleural effusion of any aetiology at diagnostic LAT between July 2010 and January 2015.

2.2.2 Study objectives and associated end points

2.2.2.1 Primary objectives and associated end points

The co-primary objectives were to determine a) the prevalence of NEL and b) the reproducibility of 3 different definitions of NEL based on visual assessment of post-drainage CXRs. The first definition is entirely subjective and is based on guidance provided by the BTS regarding the minimum extent of pleural re-apposition required to attempt pleurodesis (≥50%) The two other methods tested were defined by me and are therefore novel: Re-Expansion Proportion (REP) and Lateral Apposition Ratio (LAR). Both methods are semi-objective and their definition is described in detail in Section 3.1.3.2.

The primary end points were a) simple proportions and b) Cohen's Kappa for CXR classifications (NEL or expansile) made by 2 independent blinded assessors using each of the methods (BTS, REP and LAR).

2.2.2.2 Secondary objective and associated end points

The secondary objective was to determine whether NEL on post-drainage CXR was associated with subsequent survival. The end points used were the post-drainage CXR classifications ((NEL present or absent) for each definition (BTS, REP and LAR)), and each patient's overall survival (OS), measured from the date of LAT.

2.2.3 Study procedures

2.2.3.1 Collection of study data

A prospectively maintained departmental database was used to identify patients for inclusion. The sole inclusion criterion was the presence of a pleural effusion undergoing complete pleural drainage at LAT. Patients were excluded if there was failure to complete pleural drainage, or their age was less than 18 years, or greater than 100 years. This database included an expert 'final diagnosis' of lung re-expansion status judged at 3-month follow-up by the responsible Consultant Respiratory Physician based on all available clinical and imaging data up to that point. Electronic healthcare records were interrogated on 23rd May 2017 to add date of death, or censor, to this database.

2.2.3.2 Radiographic Measurements

For all patients and all measurements, pre-discharge CXRs demonstrating maximum lung re-expansion were selected. REP and LAR were computed independently by 2 experienced respiratory physicians (GAM, ACK) using the following methods, which are also summarised in Figure 2.1. Each was blinded to the LAT database and the other's results. To avoid recall bias, analyses using different methods were separated by a minimum of 2 weeks.

REP was defined using a method modified from that described by Rahman *et al* to approximate the area of radiographic pleural fluid opacification in the MIST-2 trial of intra-pleural enzyme therapy for pleural infection. [85] In that trial, response to treatment was quantified by the change in hemithorax pleural opacity based on measurement of regions of interest on a digital CXR. REP was similarly defined and is effectively the opposite of the pleural opacity area (see Figure 2.1).

The definition of REP (and pleural opacity area) requires the user to subjectively estimate the position and shape of the ipsilateral hemi-diaphragm in patients with any degree of pleural effusion. Since this is a significant potential source of inter-observer variation, LAR was devised to approximate the hemi-diaphragm more consistently between patients (see Figure 2.1).

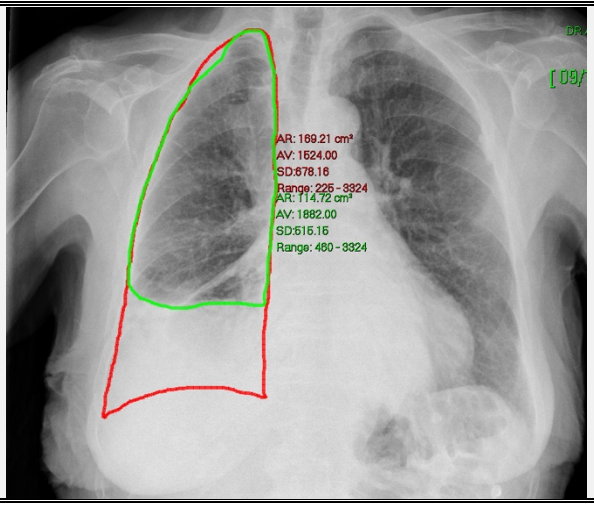
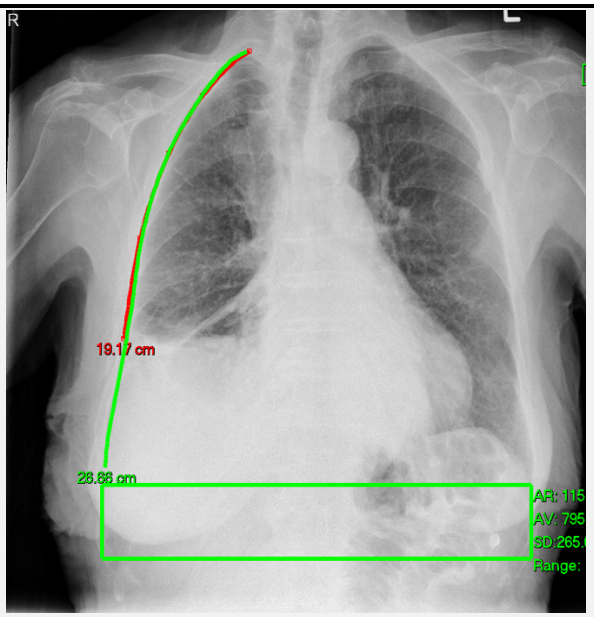
Re-expansion proportion (REP): Lung area as a proportion of total ipsilateral hemithorax area. ROIs demarcated using "free-hand" tool with user-estimation of the position of the hemidiaphragm and mediastinum.		In this example the lung area is measured at 115 cm^2 (green line) and the ipsilateral hemithorax measured at 169 cm^2 (red line) therefore: REP = 115/169 = 0.68
Lateral apposition ratio (LAR): Lateral pleural apposition length as a proportion of length of parietal pleura from lung apex to costophrenic (CP) angle. Lengths measured with "curve" tool. Where CP angle obscured by fluid, position estimated using a horizontal line traced across from the contralateral CP angle with a rectangular drawing tool.		In this example the lateral pleural length is measured at 26.7 cm (green line) and the length of pleural apposition is measured at 19.2 cm (red line) therefore: LAR = 19.2/26.7 = 0.72

Figure 2.1 Method for determining the Re-Expansion Proportion and Lateral Apposition Ratio on digital chest radiography

2.2.3.3 Classification of Radiographs as NEL or Expansile

For classification by the BTS method, the same 2 experienced respiratory physicians (GAM, ACK) independently reviewed each CXR and recorded each as showing NEL or expansile lung, based on a simple subjective assessment of whether of less than ≥50% pleural re-apposition had been achieved.

For REP and LAR, classification was based on a pre-specified statistical analysis.

2.2.4 Statistical analysis

All analyses were performed in SPSS v24.0 (Chicago, USA). A p-value of less than 0.05 was used to define statistical significance.

2.2.4.1 Primary objectives

REP and LAR measurements made by the primary operator (GAM) were used to determine the value of REP and LAR in predicting NEL (for which the reference standard was expert judgement at 3-month follow-up). These data were used to plot Receiver Operating Characteristic (ROC) curves. Optimal REP and LAR cut-points for prediction of NEL were calculated using likelihood ratios. REP and LAR data were then dichotomised around the optimal cut-point for each allowing creation of 2x2 contingency tables for 'expansile lung' or 'NEL'. A 2x2 contingency table based on the classification made by the primary operator using the BTS method was also created, allowing direct comparison between the three definitions. Inter-observer agreement using each method was assessed using Cohen's Kappa Statistic (κ) to compare the classification results by all 3 methods by the 2 operators.

2.2.4.2 Secondary objectives

Kaplan-Meier methodology was used to assess survival by re-expansion status for each approach and operator for all patients with confirmed pleural malignancy. Final censoring was undertaken on 3 October 2018. The log-rank test was used to compare differences between expansion classification.

2.3 Post-drainage radiographic identification of Non-expansile Lung and its prognostic impact – Stage 2

In stage 2 of this retrospective study, the QEUH LAT cohort (described in Section 3.1.1) was extended and then filtered to include only those patients with a final diagnosis of MPE. An external cohort from Southmead Hospital (Bristol) was also collated and analysed. Changes from the Stage 1 study protocol were approved by research ethics committee (REC) as a Substantial Amendment to the original study protocol (SA April 2018). Ethical approval for research activities at Southmead Hospital were approved by the South West – Central Bristol Research Ethics Committee (Ref: 08/H0102/11) as part of the Pleural Investigation Study. [86]

2.3.1 Patient selection

Prospectively maintained databases in Glasgow (Cohort 1) and Bristol (Cohort 2) were used to identify consecutive patients who underwent complete MPE drainage at diagnostic LAT between July 2010 and March 2018 (Glasgow), and July 2013 and July 2017 (Bristol).

2.3.2 Study objectives and associated end points

2.3.2.1 Primary objectives and associated end points

The primary objectives were to determine whether NEL on post-drainage CXR is associated with subsequent survival in a larger cohort of patients with MPE and then compare any association with recognised prognostic markers in MPE. The associated end points were a) the CXR classification (NEL or expansile) based on the BTS method (since this was associated with highest Kappa value in Stage 1), b) the total and individual components of the LENT prognostic score, and c) OS from the date of LAT.

2.3.2.2 Secondary objectives and associated end points

The secondary objectives and associated end points are shown in Table 2.1.

Table 2.1 Post-drainage radiographic identification of Non-expansile Lung and its prognostic impact – Stage 2; secondary objectives and associated end points

Secondary Objective	**Associated End Points**
To determine the inter-observer agreement associated with the BTS method of lung re-expansion classification	CXR classification using BTS method by two independent assessors in Cohort 1 and two further independent assessors in Cohort 2
To determine any prognostic association between extreme NEL (no lateral pleural apposition post-drainage) and complete re-expansion (complete apposition)	• Lung re-expansion classified into 'extreme expansion' phenotypes by subjective visual estimation • OS
BTS, British Thoracic Society; CXR, chest radiograph; NEL, non-expansile lung; OS, overall survival	

2.3.3 Study procedures

2.3.3.1 Collection of study data

A study database was created collating data from the 2 study centres as described in Section 2.3. For all patients included, the following data was retrospectively recorded using electronic NHS record systems:

- Demographics (age and gender)
- Effusion laterality
- Tumour type
- Mode of diagnosis
- The components of LENT score; pleural fluid lactate dehydrogenase level (LDH), Eastern Cooperative Group Performance Status (PS), blood neutrophil to lymphocyte ratio (NLR), LENT tumour type score. LDH, PS and NLR were recorded from the time of diagnosis. Where any of these data were not available within 28 days of diagnosis, they were recorded as missing and the case excluded from analysis
- OS recorded from date of diagnostic LAT to death (or censor)

2.3.3.2 Radiographic analyses

Post-drainage CXRs demonstrating maximal lung re-expansion pre-discharge were classified as NEL or expansile for all patients by 2 independent assessors in Cohort 1 (GAM, ACK) and a further 2 independent assessors in Cohort 2 (PH, AB) using the BTS method. All assessors were experienced respiratory physicians who routinely assess CXRs for NEL in clinical practice. An additional subjective visual judgment was used to classify patients into 3 groups; extreme NEL (no lateral pleural apposition), incomplete lateral pleural apposition, and complete re-expansion. Those with extreme NEL and complete re-expansion were termed ‘extreme expansion’ phenotypes.

2.3.4 Statistical analysis

Analyses were performed in SPSS v24.0 (Chicago, USA) and GraphPad Prism v8.0.2 (San Diego, USA). Patient characteristics and baseline variables were

tabulated by study site; differences were assessed by unpaired t-test, Mann-Whitney or Fisher's exact test as appropriate.

2.3.4.1 Primary objectives

Univariate Kaplan-Meier methodology was used to assess survival stratified by re-expansion status for each operator. Multivariable Cox regression analysis was then performed to determine the hazard ratio for death associated with a) NEL, b) a single increment in total LENT score, and c) each component of the LENT score. For this purpose, a proportional hazard model was constructed after exclusion of any co-linearity between predictor variables. The model included NEL (present/absent), in addition to the individual components of the LENT score: LDH (as a continuous variable), NLR (continuous), PS (as a categorical ordinal variable, with PS 3 and 4 grouped together) and tumour type (as a categorical variable). Tumour types were coded according to LENT classification as 0 (mesothelioma or haematological malignancy), 1 (breast, gynaecological or renal cell carcinoma) or 2 (lung cancer or any other tumour type). These analyses were repeated in Cohort 2.

2.3.4.2 Secondary objectives

In both cohorts, Cohen's Kappa statistic was used to describe inter-observer agreement for lung re-expansion classification between assessors. Univariable Kaplan-Meier methodology was used to assess survival stratified by 'extreme expansion' phenotypes.

2.3.5 Data handling

The electronic study database and CXR assessment data were stored on password protected NHS computers. Once CXR assessment and survival data were added, identifiable patient data (Community Health Index numbers) was removed from the database prior to analysis.

2.4 Pre-EDIT: A randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc Pleurodesis (EDIT) in the management of symptomatic Malignant Pleural Effusion without obvious non-expansile lung

2.4.1 Trial setting

Pre-EDIT was a single centre randomised controlled feasibility trial based at the Pleural Disease Unit (PDU) at the QEUH. The trial was sponsored by NHS Greater Glasgow & Clyde. Pre-EDIT was funded by unrestricted grants from the West of Scotland Lung Cancer Research Group and Rocket Medical (UK). All consumables related to pleural manometry were provided by Rocket Medical (UK), who had no input into the trial design or data analysis. The trial was open to recruitment for a period of 55 weeks from August 2017 to September 2018.

2.4.2 Study objectives and associated end points

2.4.2.1 Primary objective and associated end point

To determine whether it was possible to recruit and randomise 30 patients over 12 months (or 15 patients in any 6-month period) between the EDIT treatment model and TSP (standard care control group). The end point was the recruitment rate over the 12-months during which the study was open.

2.4.2.2 Secondary objectives and associated end points

Secondary objectives and associated end points are shown in Table 2.2.

Table 2.2 Pre-EDIT trial secondary objectives and associated end points

Secondary Objectives	**Secondary End Points**
To determine the feasibility of P_{EL} computation using the novel Rocket Medical DPM system	The time taken to perform the EDIT large volume aspiration, including measurement of ΔIPP using DPM, recording of ΔV and computation of P_{EL} The failure rate of the procedure, defined as the proportion of patients in whom P_{EL} cannot be computed
To determine the safety and tolerability of P_{EL} computation using the novel DPM	The occurrence of chest pain, cough or breathlessness during the procedure Adverse Events (AEs) and Serious AEs (SAEs) associated with use of the DPM
To assess the pleural fluid aspiration volume required to detect abnormal pleural elastance (where present)	The pleural fluid aspiration volume at which the rolling average pleural elastance over the preceding 250ml (P_{EL250}) first exceeds the upper limit of normal (14.5cm H_2O/L)
To determine the proportion of patients allocated to EDIT management (Group A) who require pneumothorax induction to facilitate safe ICD/IPC insertion following DPM	The proportion of patients in which pneumothorax induction is required to facilitate safe ICD/IPC insertion in the EDIT arm (Group A)
To test the assumption that pleural cavity ΔV is equivalent to the volume of pleural fluid removed during aspiration	Pleural fluid aspiration volume (ΔV_{OUT}) Pleural cavity volume change, as measured directly using volumetric MRI (ΔV_{MRI}; defined as pre- minus post-aspiration pleural cavity volume)

To test the accuracy of a predictive model of pleural effusion volume (V_{TUS}) based on thoracic ultrasound (TUS) measurements, which is a proposed inclusion criterion for the EDIT study	TUS estimated total pleural effusion volume (V_{TUS}) Pre-pleural fluid aspiration pleural cavity volume (V_{MRI})
P_{EL}, pleural elastance; DPM, digital pleural manometry; EDIT, elastance directed indwelling pleural catheter or talc pleurodesis; IPP, intra-pleural pressure; V, pleural cavity volume; ICD, intercostal drain; IPC, indwelling pleural catheter; MRI, magnetic resonance imaging; TUS, thoracic ultrasound	

2.4.3 Patient selection

Patients with symptomatic MPE were identified at cancer multidisciplinary team (MDT) meetings, routine outpatient appointments, and during inpatient reviews. The following eligibility criteria were applied:

2.4.3.1 Inclusion criteria

- Clinically confident diagnosis of MPE defined as any of the following:
    - Pleural effusion with histocytologically proven pleural malignancy **OR**
    - Pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid **OR**
    - Pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging (CT/MRI)
- Degree of breathlessness for which therapeutic pleural intervention would be offered
- Expected survival > 3 months
- Age >18 years
- Written, informed consent

2.4.3.2 Exclusion criteria

- Age < 18 years
- Females who are pregnant or lactating
- Clinical suspicion of NEL for which TP would not be offered
- Patient preference for 1st-line IPC insertion
- Previous ipsilateral failed TP
- Estimated pleural fluid volume < 1 litre, as defined by TUS based on the Goecke Model (see Appendix 7)
- Any contraindication to chest drain or IPC insertion, including:
    - Irreversible coagulopathy
    - Inaccessible pleural collection, including lack of suitable IPC tunnel site

- Any contraindication to MRI scanning, including:
    - Claustrophobia
    - Cardiac pacemaker
    - Ferrous metal implants or retained ferrous metal foreign body
    - Previously documented reaction to Gadolinium-containing intravenous contrast agent
    - Significant renal impairment (estimated glomerular filtration rate <30 ml/min)

2.4.4 Co-enrolment guidelines

Patients were excluded from entry into any other clinical trial that aimed to directly influence pleural fluid production, management or drainage for the duration of their participation within the study. Treatment decisions relating to the underlying malignancy were directed by the MDT in the usual fashion. Access to trials of systemic anti-cancer therapies was permitted. In the event of bilateral MPE, patients were only eligible for entry into the trial once.

2.4.5 Screening and recruitment

2.4.5.1 Pre-screening

Patients with symptomatic MPE were identified at cancer MDT meetings, routine outpatient appointments, and during inpatient reviews at three hospital sites within the Greater Glasgow & Clyde health board; the QEUH, the Beatson West of Scotland Cancer Centre and the Glasgow Royal Infirmary. These patients were recorded in a pre-screening log. Those patients eligible for the trial were provided with a study patient information sheet (PIS) (see Appendix 1) at the earliest opportunity. Patients pre-screened after implementation of a substantial amendment to the protocol in January 2018 also received a Treatment Preferences Survey (TPS) PIS (see Appendix 2)

2.4.5.2 Consent to formal screening

After initial introduction to the trial and receipt of the PIS, a member of the clinical team made separate contact with the patient to assess whether they wished to consider participation. This was typically done the following day. If patients were agreeable to trial involvement, a member of the research team, identified a suitable opportunity to address any questions and to seek written

informed consent (see screening consent form, Appendix 3) to attend for a formal screening visit. Where patients did not advance from pre-screening to formal screening, the reason(s) were recorded in the pre-screening log.

2.4.5.3 Formal screening, Eligibility Assessment and Consent

At the formal screening visit, all eligibility criteria were systematically examined using a checklist. This process included bedside TUS during which pleural effusion volume (V_{TUS}) was estimated based on the lateral and sub-pulmonic effusion extent using the Goecke formula. [87] Details of this estimation method are provided in Appendix 7. Patients meeting all eligibility criteria, including V_{TUS} > 1 litre, were then invited to give additional written consent to randomisation and trial enrolment (see pre-EDIT consent form, Appendix 4). A period of at least 24 hours was required between the patient receiving the study PIS and giving consent to full trial participation.

2.4.5.4 Treatment Preferences Survey consent

All pre-screened potential pre-EDIT participants were eligible for participation in the TPS following a substantial amendment to the protocol which was approved on the 9th February 2018. After sufficient time to consider their involvement, those agreeable to TPS completion gave separate informed written consent (see TPS consent form, Appendix 5). Patients were able to complete the TPS without participating in the main pre-EDIT study and vice versa.

2.4.6 Study procedures and assessments

The pre-EDIT study design and procedures are summarised in Figure 2.2.

2.4.6.1 Admission to Pleural Disease Unit

Outpatients consenting to full pre-EDIT participation were urgently admitted to the GPDU, based on ward 7b, QEUH. Those consenting to participation as QEUH inpatients were transferred to the PDU for trial-specific management. In parallel, a research MRI appointment was provisionally booked to coincide with availability of the patient and research team to facilitate delivery of study interventions within a clinically appropriate timescale (< 14 days in all cases).

2.4.6.2 Treatment Preferences Survey

TPS participants completed this simple semi-structured survey at the point of pre-screening or at a formal pre-EDIT screening visit, where performed. The TPS is shown in Appendix 6.

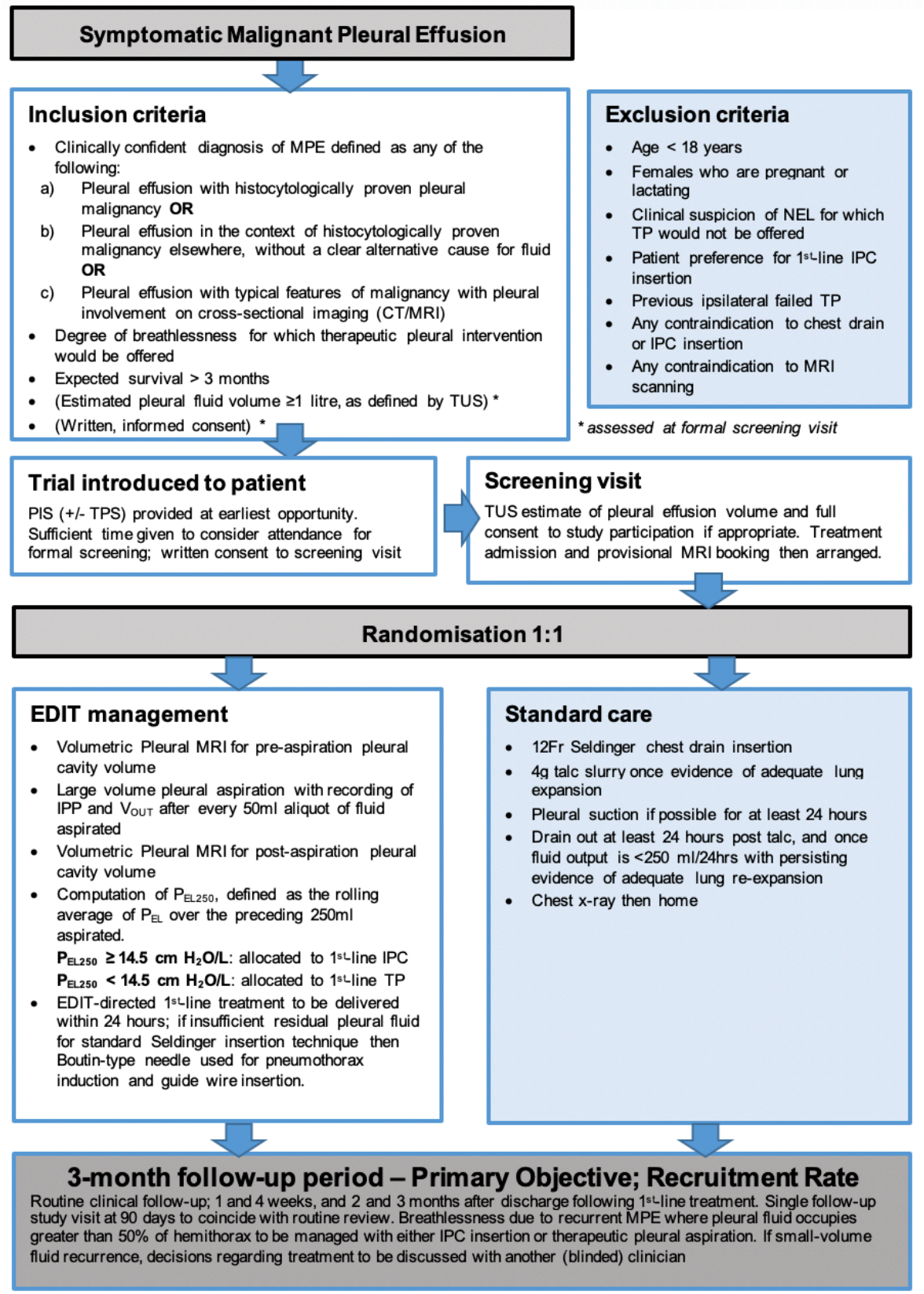


Figure 2.2 Pre-EDIT design summary; eligibility criteria, recruitment pathway, study procedures and follow-up arrangements

2.4.7 Baseline assessments

Baseline assessments were completed following full consent and recorded on the relevant CRF by a member of the trial team prior to randomisation. Data recorded included:

- patient demographics
- mode of presentation
- smoking history
- physical characteristics
- symptoms
- current diagnosis
- performance status
- current medication
- previous pleural interventions
- past medical history
- pain and breathlessness 100mm VA scores
- recent blood test results (within 10 days)
- baseline TUS findings

2.4.8 Randomisation

Randomisation was performed immediately after completion of the baseline assessments using a validated online system (www.sealedenvelope.com). Patients were allocated 1:1 using random permuted blocks into one of two groups:

A: EDIT management

B: Standard Care

Minimisation or stratification was not used in pre-EDIT. However, the availability of complete participant LENT scores at the time of randomisation was recorded since this is a major prognostic indicator which may be used to minimise imbalance between groups in a subsequent definitive EDIT study.

2.4.9 Post randomisation

Definitive pleural management according to group allocation was implemented within 72 hours of allocation and followed trial specific instructions (TSIs) (see Appendices 7-9).

2.4.10 Standard Care

Following procedure-specific written consent (recorded on generic NHS GG&C consent forms), a 12Fr ICD was placed at a bedside TUS-marked site under strict aseptic conditions using a Seldinger technique. Details of the drain insertion were recorded in the study intervention case report form (CRF). Passive pleural drainage was performed at a rate not exceeding 1000ml/hour. A post-insertion chest radiograph (CXR) was performed.

A repeat CXR was performed 18-24 hours after ICD insertion; if there was no evidence of NEL or significant residual pleural fluid then TSP was attempted. Pre-medication with oral morphine (Oramorph 10mg) and intra-pleural 1% lidocaine (3mg/kg) was given 10 minutes prior to intra-pleural administration of a sterile slurry comprising 4g sterile graded talc (Novatech SA, France) suspended in 50ml 0.9% sodium chloride solution. After slurry installation and a 2-hour period of ICD clamping, patients were placed on thoracic suction using a Thopaz ambulatory suction unit, if available. Suction was commenced at -10 cmH_2O and titrated to -20 cmH_2O, if tolerated. Pleural drainage volumes were recorded at least 8 hourly. Twice daily 0.9% sodium chloride solution ICD flushes were delivered from the time of insertion to the time of removal. The ICD was left in situ for at least 24 hours after the talc slurry had been administered and removed once the fluid output fell below 250ml in the preceding 24-hour period. A CXR was performed following ICD removal prior to discharge.

Where NEL or residual fluid was identified, ICD patency was assessed by flushing. Thoracic suction was applied at the discretion of the primary physician. An additional CXR was repeated after 18-24 hours. Talc slurry was administered once at least 50% visceral and parietal pleural re-apposition was achieved based on visual estimation. Where NEL persisted within 48 hours of ICD placement, further management was at the discretion of the primary physician. Patients in this situation remained in the study and were followed up as planned.

2.4.11 EDIT management

The EDIT management pathway is summarised is Figure 2.3 overleaf.

2.4.11.1 Pre-DPM TUS

On completion of MRI scanning, participants were transferred back to the Clinical Research Facility and a TUS scan was performed by me. Where possible, a Siemens Acuson SC2000 US machine with 6C1 HD curvilinear array (1.5 - 6.0 MHz) was used. If this machine was unavailable, a Sonosite M-Turbo with C60xi curvilinear array (2.0 – 5.0 MHz) was utilised. Full procedural details are shown in the combined TUS/DPM TSI (Appendix 7). In brief, pre-DPM TUS scanning comprised of 3 stages: estimation of pleural effusion volume (V_{TUS}) using the Goecke method, [87] M-mode cardiac impulse transmission assessment of the atelectatic lung during breath holding, and finally, identification and marking of a safe DPM catheter insertion site.

M-mode image analysis was undertaken following completion of DPM. The maximal atelectatic lung excursion observed during a breath hold at the end of tidal expiration (functional residual capacity) was measured over 3 separate cardiac cycles and a mean of these values recorded on the study CRF. Images acquired on the Siemens Acuson SC2000 were analysed with integrated Siemens software and a specific m-mode measurement tool. Images acquired using the Sonosite M-Turbo were exported in Digital Imaging and Communications in Medicine (DICOM) format and analysed in Horos v3.3.3 (an open source medical image viewer) using the generic ‘Length’ tool. An example is shown in Figure 2.4.

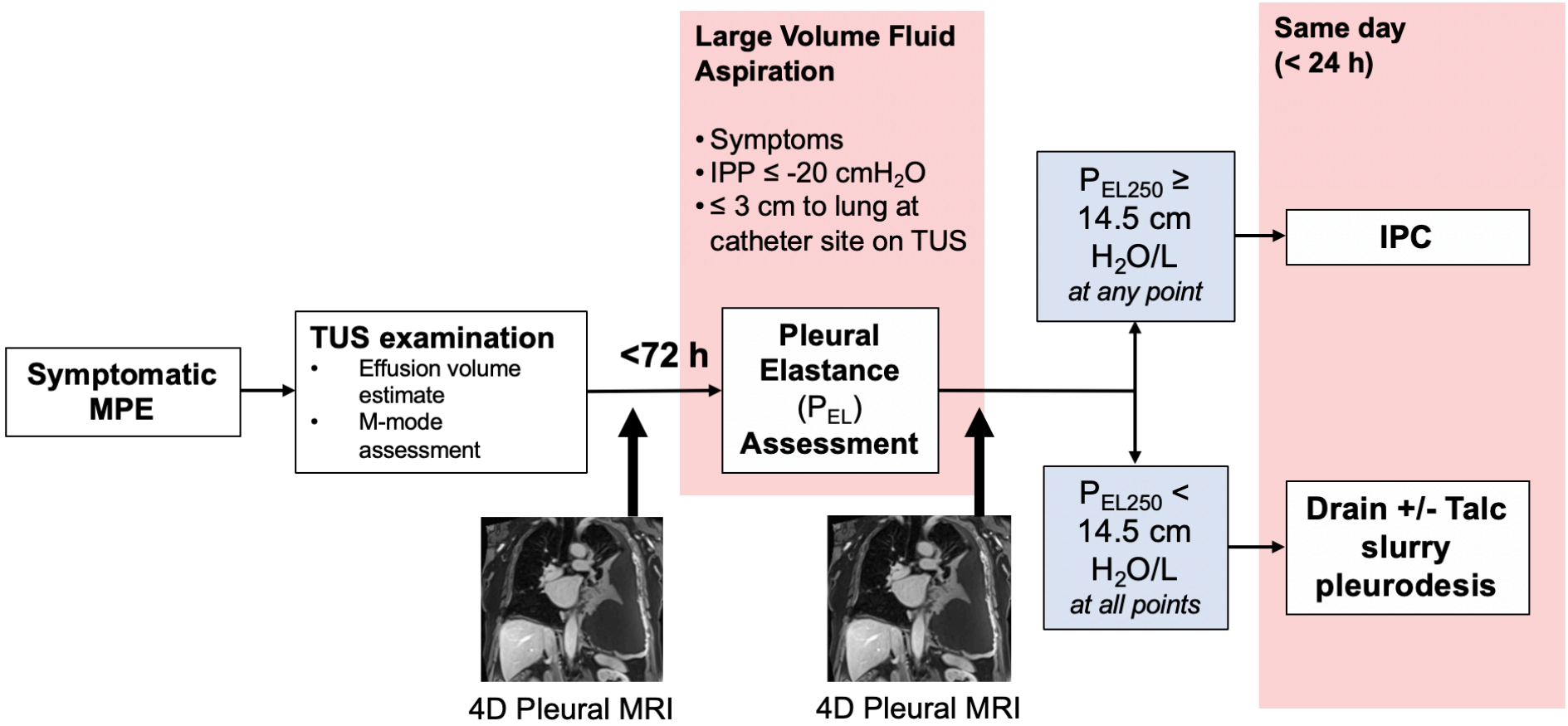


Figure 2.3 The EDIT management treatment pathway delivered within the pre-EDIT study

MPE, malignant pleural effusion; TUS, thoracic ultrasound scan; IPP, intrapleural pressure; P_{EL}, pleural elastance; MRI, magnetic resonance imaging; IPC, indwelling pleural catheter. MRI volumetric analyses are presented in Chapter

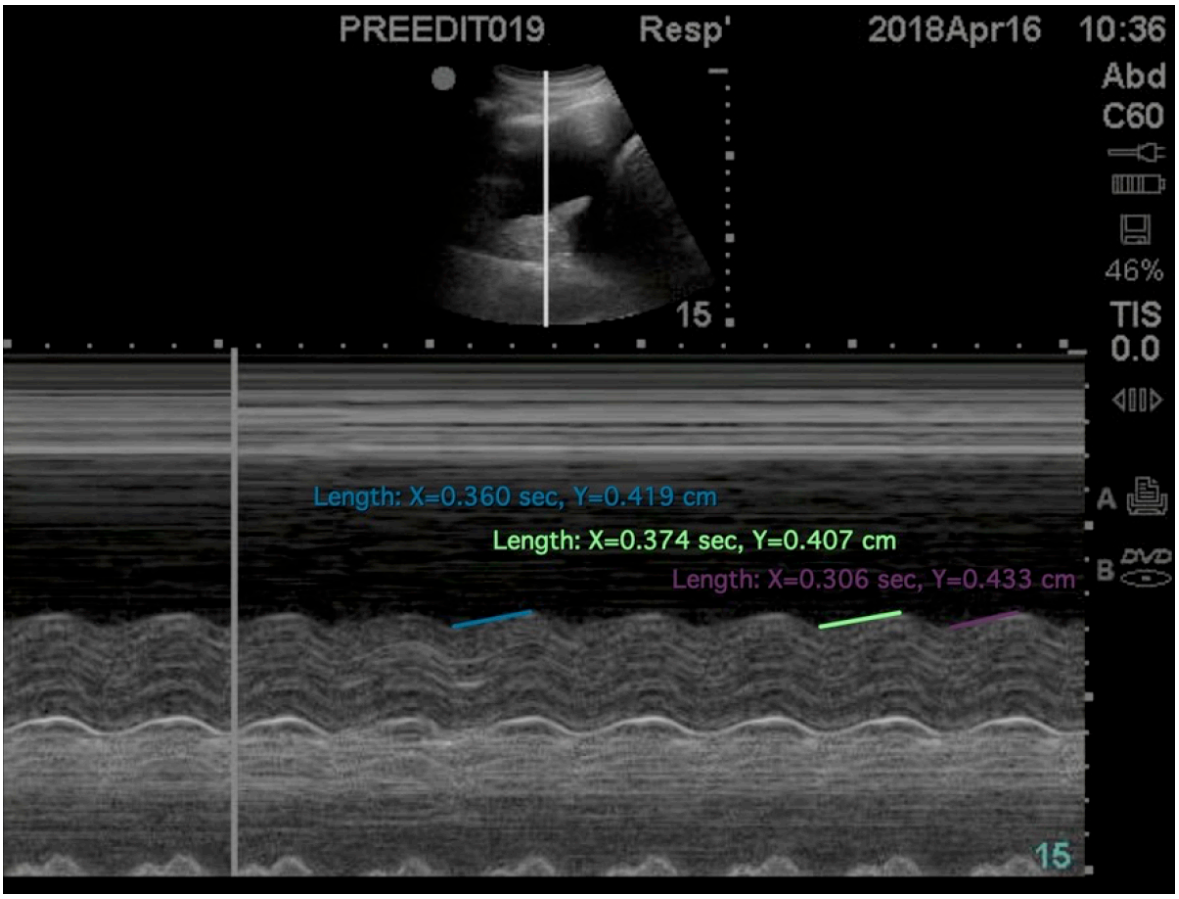


Figure 2.4 M-mode TUS image in pre-EDIT subject 19 acquired during a breath hold at functional residual capacity using a Sonosite M-Turbo/C60xi curvilinear array showing atelectatic lung excursion measurements made in Horos v3.3.3

2.4.11.2 Pre-DPM MRI scanning

Patients attended the Clinical Research Imaging Facility within the Institute of Neurological Sciences at the QEUH. An MRI safety checklist was completed by a member of the research imaging team. Informed written consent specifically relating to MRI scanning was then recorded. All MRI scans were performed using a 3.0T Siemens PRISMA® MRI scanner.

Pre-DPM, the affected thoracic cavity was localised, and an isotropic T1-weighted volume acquired using volumetric interpolated breath-hold examination (VIBE) sequences. A stack of axial slices covering the entire lung and surrounding pleura was acquired as a set of short breath-holds. Time-resolved 3D MR imaging of the complete thorax was then obtained during tidal free-breathing and maximal inspiratory/expiratory efforts. A modified time-resolved angiography with interleaved stochastic trajectories (TWIST) sequence

was utilised for this purpose. Following this, Gd-DTPA contrast (Gadovist) was administered as a 15-40 ml bolus (0.05 mmol/kg). VIBE sequences were reacquired at copied slice positions to provide comparative post-contrast images at multiple time points.

2.4.11.3 DPM and computation of P_{EL250}

Procedure-specific informed written consent for DPM was taken (recorded on generic NHS GG&C consent form). Under strict asepsis, the Rocket Medical DPM aspiration catheter was inserted following the detailed TSI shown in Appendix 7. Opening end expiratory IPP measurement was recorded. Pleural fluid was then removed in 50ml aliquots until any of the following occurred:

- the patient developed chest discomfort or excessive coughing
- an intra-pleural pressure of ≤ -20cmH_2O was reached
- target aspiration volume reached

The target aspiration volume was initially defined by subtracting 500ml from the estimated total pleural effusion volume estimated by the Goecke TUS equation, see Appendix 7. [87] Following early experience in the delivery of EDIT management, this method was changed to intermittent mid-procedure TUS assessment with aspiration terminated when a horizontal costal-lung distance of ≤ 30mm was reached. This amendment to the protocol is discussed further in Section 4.3.3.3.

Sequential end expiratory IPP measurements were recorded after each 50ml aliquot. Additionally, the highest and lowest IPP values recorded during maximal respiratory manoeuvres at aspiration volumes of 200ml, 500ml and 1000ml were recorded. Post procedure, P_{EL250}, the rolling average of P_{EL} over the preceding 250 ml of fluid removed was calculated at each 50ml interval. The highest recorded P_{EL250} in each case ($MaxP_{EL250}$) was documented on the intervention CRF. At the end of the aspiration procedure, the mass of drained pleural fluid with its associated drainage bag and tubing was recorded.

2.4.11.4 Post-DPM MRI scanning

Following DPM, patients returned to the Clinical Research Imaging Facility to undergo a further MRI scan. Again, the affected thoracic cavity was localised, and a post-aspiration isotropic T1-weighted volume acquired using VIBE sequences. Repeat TWIST imaging of the complete thorax during tidal free-breathing and maximal inspiratory/expiratory efforts was performed but further Gadovist administration and contrast-enhanced imaging was not undertaken.

2.4.11.5 Definitive intervention

Definitive pleural management was instigated within 24 hours of DPM and, where possible, on the same day. Definitive management was allocated based entirely on the recorded $MaxP_{EL250}$ as follows:

$MaxP_{EL250}$ ≥ 14.5 cm H_2O/L: allocated to 1st-line IPC

$MaxP_{EL250}$ < 14.5 cm H_2O/L: allocated to 1st-line ICD and TP

Note that the rationale in selecting this threshold is described in the Introduction (Chapter 1, Section 1.8.3) and in Chapter 4 (pre-EDIT Results, Section 4.1.5).

Separate procedure specific informed written consent was recorded prior to the allocated intervention and documented on generic NHS GG&C consent forms. Pre-intervention, a further TUS scan was performed to determine whether sufficient residual fluid, in the judgment of the operator, remained to allow safe ICD or IPC placement using a standard Seldinger insertion technique. All interventions were performed in single rooms within the PDU in accordance with the appropriate TSI (Appendix 8 relates to ICD insertion and Appendix 9 relates to IPC insertion).

In cases of insufficient residual fluid to safely allow a standard Seldinger insertion, the 1st-line allocated procedure was delivered using a Boutin-type needle to provide blunt pleural access. This was performed with the patient in a lateral decubitus position and allowed formation of an iatrogenic pneumothorax with minimal risk of visceral injury. The standard Seldinger guidewire was then introduced into the pleural space and the remainder of the procedure was completed in the usual fashion. Finally, a CXR was performed post-procedure to assess the drain position.

2.4.11.6 Post intervention

Where 1st-line IPC insertion was performed, subsequent management followed local practice. This comprised overnight admission for observation on the evening of insertion and IPC drainage immediately post insertion, the evening of insertion and the following morning before discharge. Domiciliary IPC drainage was initially performed daily with sequential reductions in drainage frequency if/when volumes reduced. In those patients undergoing elastance-directed ICD

insertion +/- TSP, on-going management was identical to those patients receiving Standard Care.

2.4.12 Estimation of pleural fluid aspiration volume during DPM

The total pleural fluid volume removed during DPM (V_{OUT}) was estimated as follows:

$$V_{OUT} = (M_{TOTAL} - M_{BAG}) / SG$$

M_{TOTAL} = mass of aspirated fluid and associated drainage bag/tubing

M_{BAG} = mass of drainage bag/tubing

SG = estimated specific gravity of pleural fluid based on protein concentration, based on a prior publication [88]

Where:

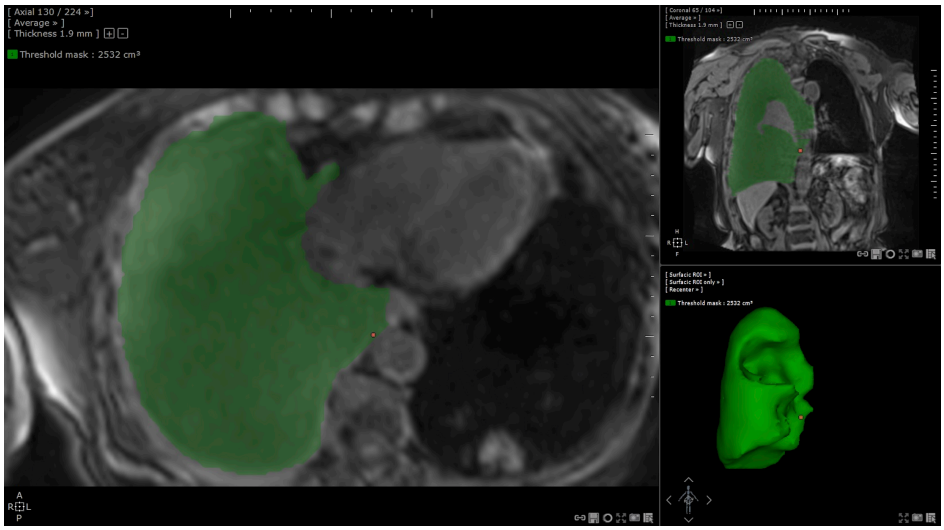
$$SG = P / 353 + 1.0076$$

P = pleural effusion protein content in g/L

2.4.13 Computation of pleural cavity volume change on MRI

MRI scans were used to provide a 'gold standard' measure of pleural cavity volume. The change in pleural cavity volume was calculated as the difference between pre- and post-DPM pleural cavity volumes assessed on MRI (ΔV_{MRI}). For this purpose, T1 weighted isotropic VIBE sequences were analysed by semi-automated segmentation using Myrian® software (Intrasense, Paris, France). This required the manual application of a threshold contour to every fourth or fifth axial slice. A threshold mask extrusion algorithm was then launched to interpolate the pleural cavity between marked slices. The volume of the pleural cavity was automatically calculated by the software multiplying the sum of voxels within the extrusion mask and the known voxel volume. An example threshold contour and complete threshold mask is shown in Figure 2.4. A blinded second assessor (WH, ST5 Radiology) repeated volumetric measurements for assessment of inter-rater reproducibility.

(a) Pre-aspiration



(b) Post-aspiration

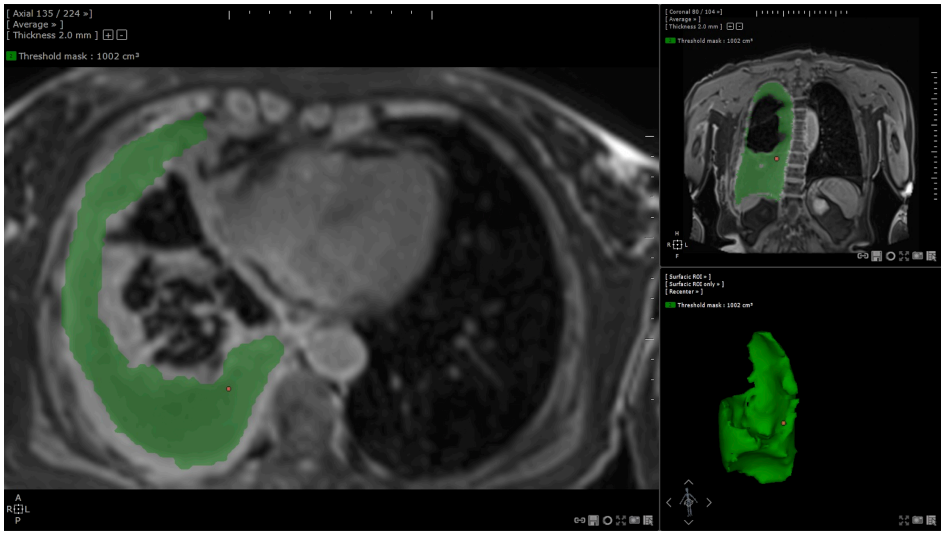


Figure 2.5 Screenshots from Myrian® software (Intrasense®, Paris, France) showing T1 VIBE axial and coronal images with an overlying extruded threshold mask of the pleural cavity and associated 3-dimensional reconstruction.

2.4.14 MRI Phantom

To provide a reference standard for MRI volumetric data acquired in pre-EDIT a deformable trial-specific pleural cavity MRI phantom (see Figure 2.5) was developed by collaborators from the NHS MR Physics Group, NHS Greater Glasgow and Clyde. The phantom comprised an acrylic frame containing a 2L latex bag (analogous to the parietal pleura), in which a smaller 1L latex bag

(analogous to the visceral pleura) was placed. Both bags were attached to the frame by their necks and connected to independent tubes to allow filling with known volumes of water and air, respectively. At the foot of the frame an adjustable piston plate formed a simulated ‘diaphragm’. The phantom was repeatidly imaged according to the pre-EDIT MRI protocol while containing a range of fluid volumes from 300ml – 1000ml. This work was performed entirely by collaborators from the NHS MR Physics Group (MSc student Saumya Josan, co-supervised by Drs Mark McJury and John Foster), but described in my thesis since it was essential to the validity of my MRI volumetric studies.

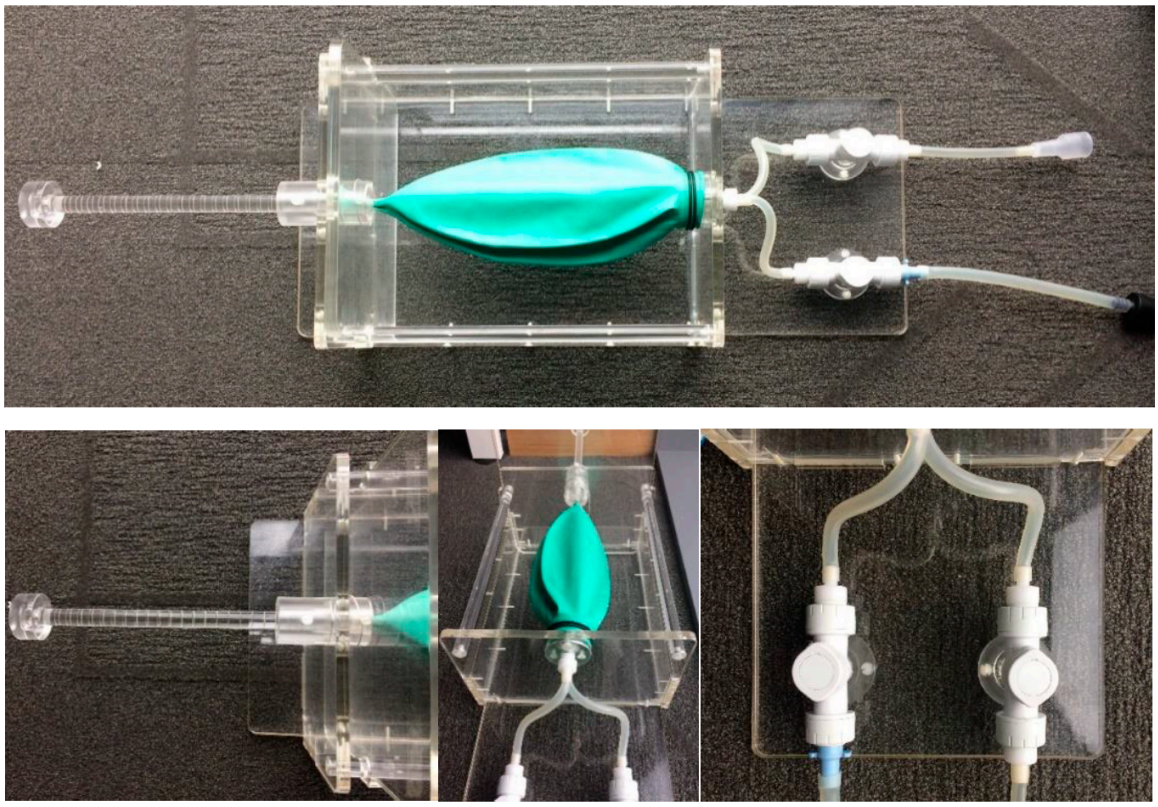


Figure 2.6 Pre-EDIT MRI Phantom

Reproduced with permission from Ms Saumya Josan, Dr Mark Majury and Dr John Foster, NHS MR Physics Group, Queen Elizabeth University Hospital, Glasgow

2.4.15 Visual assessment scoring

Visual analogue (VA) scores for chest pain and breathlessness were documented as part of baseline assessments for all study participants and then daily for 7 days following ICD or IPC placement. Participants were asked to complete these scores at approximately the same time each day. Following this, patients were asked to complete VA scores weekly on a specific document.

Patients were instructed not to complete VA scores retrospectively with the exception of weekly scores which could be completed within 48 hours. Omission of daily VA scores, or weekly VA scores not completed within 48 hours, were treated as missing data.

2.4.16 Radiographic definition of NEL

Lung re-expansion following trial interventions was assessed by me using subjective visual estimation. In those patients receiving TSP, the post-ICD removal, pre-discharge CXR was assessed. In those who underwent IPC insertion, the CXR obtained 14 days from discharge was assessed to avoid false positive NEL classification due to unavoidable air ingress during the IPC insertion procedure. Radiographs were classified as showing:

- Expansile lung (>75% expansion)
- NEL_{75} (<75% but >50% expansion)
- NEL_{50} (<50% expansion)

2.4.17 Follow-up arrangements

Patients in both treatment groups were offered routine clinical appointments at approximately 7, 28, 60 and 90 days from discharge, with an additional visit 14 days from discharge for those managed with IPC. A single trial follow-up visit at 90 days (+/- 10) was arranged to coincide with clinical appointments, where possible, or completed by review of electronic records. At this research visit, a chest radiograph was acquired and details of the number of hospital admissions, repeat pleural interventions, clinic visits and survival status was recorded based on clinical history (if available), augmented by NHSGGC electronic records systems (Clinical Portal and PACS). Electronic review of case records +/-

telephone visit was used to collect these details for patients unfit to attend clinic.

2.4.18 Recurrent breathlessness following study intervention

In the event of urgent hospital admission during the follow-up period, emergency management, including further pleural procedures, was not restricted by study participation and delivered at the discretion of the responsible acute team according to standard practice.

Where study participants experienced sub-acute recurrent breathlessness during trial follow-up, comprehensive clinical and radiological (CXR / TUS) assessment by the research team was undertaken to elucidate the likely cause. All trial participants were provided with direct contact details for a clinical nurse specialist to facilitate early review in the event of symptoms developing between review appointments.

Where recurrent MPE was identified and occupied greater than an estimated one third of the hemithorax on CXR, further pleural intervention in the form of IPC insertion or therapeutic pleural aspiration was offered where clinically appropriate. In the event of smaller volume MPE recurrence, further management was discussed with a second respiratory physician blinded to trial group allocation. Further pleural intervention was offered where a consensus was achieved.

2.4.19 Trial images

All CXR, CT and MRI images relating to trial participation have been securely stored on NHS Picture Archiving and Communication Systems (PACS) in line with routine clinical practice. Representative TUS images and m-mode cine clips have been stored on an encrypted study hard drive.

2.4.20 End of trial

Trial recruitment was completed on 18th September 2018, approximately 55 weeks after opening, at which point 30 patients had been recruited, randomised and completed their allocated pleural management. Trial participation ceased on 13th December 2018 when all patients had completed their 90-day study follow-up visit or were deceased.

2.4.21 Bias reduction

Blinding of patients or clinicians to trial group allocation was not attempted as a 'sham' DPM procedure would be associated with an unacceptably high degree of clinical risk. The researcher performing DPM was clearly aware of group allocation and excluding them from further involvement in the participant's care, to facilitate blinding of a separate clinician providing ongoing care, was considered impractical. The influence of potential bias was minimised through use of objective and prescriptive TSIs for the peri-procedural management within each arm of the trial.

2.4.22 Schedule of study activity

A schedule of study activity is shown in Figure 2.5

Visit Number			**1**	**2**	**3**	**4**	**5**	**6**	**VAS only**	**VAS only**	**7**	**8**	**9**
Approximate Study Day			0-13	11 (+/-3)	14	14-15	15-21	22-28 (+/-4)	28-34 (+/-2)	35-41 (+/-2)	43-49 (+/-4)	75-81 (+/-7)	105-111 (+/-10)
Pre-enrolment													
Identification of potentially eligible patient and add to pre-screening log			X										
Pre-screen failure: Provide TPS PIS, take TPS consent and complete TPS			X										
Pre-screen success: Provide main study PIS and TPS PIS, address questions and take consent for screening			X										
Screening visit: review eligibility criteria (including TUS assessment) and complete TPS				X									
Full consent to enrolment				X									
Post-enrolment													
Baseline assessments				X									
Randomisation				X									
Admission for Intervention													
EDIT management		**Standard Care**											
Pleural MRI pre-DPM		ICD insertion, pleural fluid sampling and TP			X								
TUS and target volume calculation					X								
DPM and pleural fluid sampling					X								
Pleural MRI post-DPM					X								
Normal P_{EL}	**Elevated P_{EL}**												
ICD and TP	IPC					X							
Discharge following intervention							X						
Follow-up (all patients)													
CXR					X	X	X	X			X	X	X
VAS scores					X	X	X	X	X	X	X		
Routine clinic visits								X			X	X	X
Study visit													X

Figure 2.7 Pre-EDIT study schedule of activities

2.4.23 Patient Withdrawal

Patients were withdrawn from the study if any of the following occurred:

- Patient withdrawal of consent
- Patient no longer fit for therapeutic pleural aspiration, DPM or ICD insertion
- Clinical opinion of the doctor that the patient should withdraw

2.4.24 Statistical Considerations

2.4.24.1 Sample Size

As a feasibility study, pre-EDIT did not seek to test the efficacy of EDIT management and therefore a formal sample size calculation was not performed. Instead, it was proposed that recruitment of 30 patients would provide a reasonable view of the barriers which might be met in delivering EDIT management and provide adequate opportunity to explore possible solutions to problems encountered.

The data collected on survival, 90-day failure rate, and recruitment (including any drop-outs) may potentially contribute to a future sample size calculation for a full scale phase III trial aiming to detect a clinically meaningful reduction in failed 1st-line treatment of MPE.

2.4.24.2 Statistical Analysis Plan

The following data analysis plan was included in the trial protocol:

- The demographic and clinical characteristics of the study population were described using means (with standard deviations) or medians (with inter-quartile ranges) to summarise continuous variables and proportions to summarise categorical variables.
- The primary objective of recruitment rate was estimated as the number of patients recruited, divided by the number of patients identified as eligible pre-screening and will be expressed as a rate per month.
- The time taken to perform DPM, the failure rate of DPM and the incidence of AEs and SAEs associated with DPM and definitive intervention were reported by simple descriptive statistics or proportions where appropriate.

- Simple descriptive statistics were also used to report the aspiration volume required to detect abnormal P_{EL}.
- The number of patients who require pneumothorax induction for ICD/IPC insertion was reported as a proportion.
- The agreement between ΔV_{OUT} and ΔV_{MRI} measurements was examined using the Bland-Altman method.
- The agreement between V_{TUS} and V_{MRI} pre-DPM measurements was examined using the Bland-Altman method.

Post hoc, the following analyses were performed:

- 2x2 Contingency Tables were used to assess the sensitivity and specificity of *high* P_{EL} for NEL_{50} expressed as percentages with 95% confidence intervals. Statistical analyses were performed using GraphPad Prism v8.0.2 (San Diego, USA).

- M-mode excursion data and associated post-drainage final radiographic lung expansion classification data were used to plot receiver operator characteristic (ROC) curves. The diagnostic performance of M-mode lung excursion for NEL_{50} and NEL_{75} was expressed as area under the ROC curve. This analysis was performed in SPSS v24.0 (Chicago, USA).

2.4.25 Safety Reporting

All Adverse Events were reported directly to the trial sponsor.

2.4.25.1 Adverse Event (AE)

An adverse event is any untoward medical occurrence that the patient experiences whilst participating in a clinical trial. This includes occurrences that are not necessarily caused by or related to the trial intervention. All AEs were recorded in the patient's medical records as they were reported. Full details of AEs including the nature of the event, start and stop dates, severity, relationship to study intervention and outcome were recorded. AEs were followed until resolution.

2.4.25.2 Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined where an AE is associated with any of the following, whether or not considered related to the trial intervention:

- Results in Death
- Life-threatening (i.e. at the time of the event)*
- Requires inpatient hospitalisation or prolongation of existing hospitalisation†
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is considered medically significant by the Investigator‡

*Life threatening means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.

†Requires in-patient hospitalisation should be defined as a hospital admission required for treatment of an adverse event.

‡Considered medically significant by the Investigator are events that may not result in death, are not life threatening, or do not require hospitalisation, but may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above.

2.4.26 SAEs Related to Study Procedures

Related SAEs were defined as any SAE that was reported as possibly, probably or definitely related to the use of the DPM, subsequent pleural procedures in Group A (EDIT) patients or administration of gadolinium contrast. Table 2.3 shows the definitions used when assessing the nature of the relationship between any SAEs occurring and pre-EDIT study procedures.

2.4.27 SAEs Related and Unexpected

Any SAEs that were related to the use of the DPM, subsequent pleural procedures in Group A (EDIT) patients or the administration of gadolinium contrast and were not an expected event for this substance were subject to expedited reporting to the Main Research Ethics Committee.

Table 2.3 Definitions of SAE relationship to trial procedures

Relationship	**Description**
Unrelated	There is no evidence of any causal relationship
Possible	There is some evidence to suggest a causal relationship (e.g. the event occurs within a reasonable time after undergoing a study procedure), however the influence of other factors may have been contributed to the event (e.g. the patient's clinical condition, other concomitant treatments)
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out

2.4.28 Compliance, Audit and Protocol Deviations

2.4.28.1 Good Clinical Practice

This study was conducted in accordance with the protocol, the Sponsor's standard operating procedures, national regulatory requirements, provisions of the relevant ethics committees and Good Clinical Practice (GCP) principles.

2.4.28.2 Audits

An independent internal Glasgow Clinical Research Facility audit of compliance with the principles set out in Section 2.8.1 was undertaken on 24th July 2018. The study may be subject to additional future audit by NHS GG&C under their remit as Sponsor.

2.4.28.3 Protocol Deviation Reporting

A protocol deviation is any departure from the approved protocol. All deviations were recorded and reported to the sponsor.

2.4.29 Data Handling

Data generated by the study was stored in a linked anonymised fashion on a password-protected computer. Subject paper notes were stored in a locked filing cabinet in a locked office of a secure building. Case report forms from the trial were stored in line with current regulatory requirements. Other essential documents (including source data, consent forms, and regulatory documentation) have been archived, in an appropriate archive facility in line with current regulatory requirements and made available for monitoring, audit and regulatory inspection as required.

Chapter 3

POST-DRAINAGE RADIOGRAPHIC IDENTIFICATION OF NON-EXPANSILE LUNG AND ITS PROGNOSTIC SIGNIFICANCE

3 Chapter 3: Post-drainage radiographic identification of non-expansile lung and its prognostic significance

3.1 Introduction

MPE may be complicated by NEL, resulting in pleurodesis failure, recurrent symptoms and additional pleural interventions. Radiographic detection of NEL following initial thoracentesis, or post-ICD insertion, is an essential element of bedside decision-making when planning admission for TSP or deciding whether or not to instil talc once a patient has committed to a pleurodesis attempt. Furthermore, limited data exist regarding the prevalence and prognostic significance of NEL. Any impact on survival should also be considered in the rational design of future MPE trials.

At present, a universally accepted definition of NEL does not exist. In current clinical practice, radiographic visual estimation of lung re-expansion is used to identify NEL. This approach is subjective and based on varying thresholds of re-expansion favoured by individual clinicians. However, a widely accepted minimum pleural apposition standard prior to attempting talc instillation is derived from a consensus statement in the 2010 BTS pleural guideline suggesting that pleurodesis is unlikely to be successful where less than half of the visceral and parietal pleura are in contact. [4] The reproducibility of this judgment is unknown but such a subjective assessment is vulnerable to inconsistency between (and within) readers, with resulting adverse effects on patient care. Greater objectivity in the method of judging NEL may improve inter-observer reliability and the consistency of clinical decision making. This in turn may improve the quality of reporting regarding the prevalence of NEL and its impact on survival in MPE studies.

In this retrospective cohort study, I evaluated two novel semi-objective radiographic definitions of NEL (termed REP (re-expansion proportion) and LAR (lateral apposition ratio)), relative to the ‘BTS Method’ and rigorously assessed the prognostic value of the most reproducible of these.

In Stage I, REP and LAR were assessed followed by a univariable survival analysis based on the most reliable definition and data from a single centre. In Stage II, a

multivariable survival analysis was performed and the results of this validated in an independent cohort from another centre. The specific objectives and associated outcome measures for Stages 1 and 2 are detailed in Chapter 2, Sections 2.2.2 and 2.3.2.

3.2 Materials and methods

A detailed description of materials and methods for this work is provided in Chapter 2, Sections 2.2 and 2.3. A brief summary follows.

3.2.1 Stage 1

A cohort of patients undergoing local anaesthetic thoracoscopy (LAT) at the Glasgow Pleural Disease Unit between July 2010 and January 2015 was studied retrospectively. All cases had been categorized as NEL present or absent during the prospective recording of data for routine service evaluation. This judgment was made after 3 months follow-up by the pleural consultant in charge of the patients care and was based on all available clinical and imaging data. Survival status of included patients with confirmed diagnosis of pleural malignancy was assessed in May 2017 using electronic records.

3.2.1.1 Radiographic Analyses

Pre-discharge chest radiographs (CXRs) showing maximal re-expansion were assessed by 2 experienced respiratory physicians (GAM, ACK) using two semi-objective definitions of NEL (REP and LAR) and the BTS visual estimation method. Details are provided in Section 2.2.3.2.

3.2.1.2 Statistical Analyses

Data recorded by the primary operator (GAM) was used to determine the predictive value of REP and LAR for subsequent NEL (expert 3-month classification) by plotting Receiver Operating Characteristic curves. Optimal cut-points for NEL were calculated using likelihood ratios allowing patients to be classified as having ‘expansile lung’ or ‘NEL’ based on their REP and LAR data. Inter-observer agreement was calculated as a proportion for continuous data (raw REP and LAR data) and using Cohen’s Kappa Statistic for all methods (dichotomised REP and LAR classification, and BTS classification). 2x2 contingency tables generated using the primary operator’s REP, LAR and BTS method data, were used to calculate the predictive value of each for subsequent NEL (expert 3-month judgement). Kaplan-Meier methodology was used to assess survival by re-expansion status for each approach and operator in those patients with confirmed pleural malignancy.

3.2.2 Stage 2

Prospectively populated databases were used to identify consecutive patients treated at two UK pleural tertiary referral centres (Glasgow Queen Elizabeth University Hospital and Bristol Southmead Hospital) who underwent complete MPE drainage during diagnostic local anaesthetic thoracoscopy (LAT) between July 2010 and March 2018 (Glasgow, Cohort 1; an extension of the cohort utilised in Stage 1 which was filtered to include only patients with malignant pleural effusion), and July 2013 and July 2017 (Bristol, Cohort 2). Demographics and LENT MPE prognostic score components (pleural fluid lactate dehydrogenase (LDH), performance status (PS), blood neutrophil-to-lymphocyte ratio (NLR), tumour type) acquired at/within 28 days of LAT were recorded. OS was recorded from LAT to death (or censor). Cases with missing data were excluded.

3.2.2.1 Radiographic Analyses

The presence or absence of NEL was evaluated on the post-LAT, pre-discharge CXR that showed the maximum expansion as judged by primary assessors at each site (GAM; PH) using the previously described BTS method. Blinded secondary assessors (ACK; AB) independently classified the same CXRs using the same definition. *Post hoc*, CXRs were further sub-classified by a single assessor at each site into extreme expansion phenotypes; 'Complete NEL' (where no lateral pleural apposition was achieved) and 'Complete Expansion' (where total pleural apposition was achieved).

3.2.2.2 Statistical Analysis

Inter-observer agreement regarding NEL, between primary and secondary assessors at each site, was quantified by Cohen's Kappa statistic. Kaplan-Meier curves and multivariable Cox regression (*a priori* model inputs: LDH, PS, NLR, LENT tumour risk score, NEL) were used to identify any association between the presence of NEL, as defined by the primary assessor, and OS in each cohort. For this purpose, Cohort 1 was used as a test set and Cohort 2 as an independent validation set. In a subsequent post hoc analysis, differences in OS between extreme re-expansion phenotypes ('Complete NEL' vs 'Complete Expansion') were compared using Kaplan-Meier methodology.

3.3 Results

The structure of the study, sequence of analyses and number of cases included in each analysis is summarised in Figure 3.1.

3.3.1 Optimal NEL definition and univariable survival analysis (Stage 1)

3.3.1.1 Study population

Ninety-three post-LAT CXRs were analysed. Based on the expert judgement at 3 months, the overall incidence of NEL was 18/93 (19%). 65 patients (70%) had a diagnosis of MPE and, of these, 10/65 (15%) required a further pleural intervention within 3 months of definitive pleural management performed during LAT admission. Demographics and final diagnoses are summarised in Table 3.1.

3.3.1.2 Radiographic NEL definitions: inter-observer agreement

The mean inter-observer difference in REP was 8% (range 0 – 39%, standard deviation (SD) 7.5%) whereas the mean inter-observer difference in LAR was 17% (range 0 – 86%, SD 21%). Following application of optimal cut-points to the continuous data (NEL defined as REP <90% or LAR <0.67), inter-observer agreement (κ) for REP, LAR and the BTS method were 0.46, 0.53 and 0.68, respectively.

3.3.1.3 Radiographic NEL definitions: prediction of 3-month expert judgement

REP predicted NEL with a sensitivity of 0.61 (95% Confidence Interval (CI) 0.49 - 0.72) and specificity of 0.94 (95% CI 0.73 – 1.00). LAR predicted NEL with a sensitivity of 0.56 (95% CI 0.44 – 0.67) and specificity of 0.94 (95% CI 0.73 – 1.00). Finally, the BTS method predicted NEL with a sensitivity of 0.81 (95% CI 0.71 – 0.89) and specificity of 0.87 (95% CI 0.81 – 1.00).

3.3.1.4 Prognosis in patients with MPE stratified by lung re-expansion status

Sixty-five patients (70%) had a confirmed diagnosis of pleural malignancy. Survival data for all patients with MPE classified by expansion status is shown for each method and assessor in Figure 3.2.

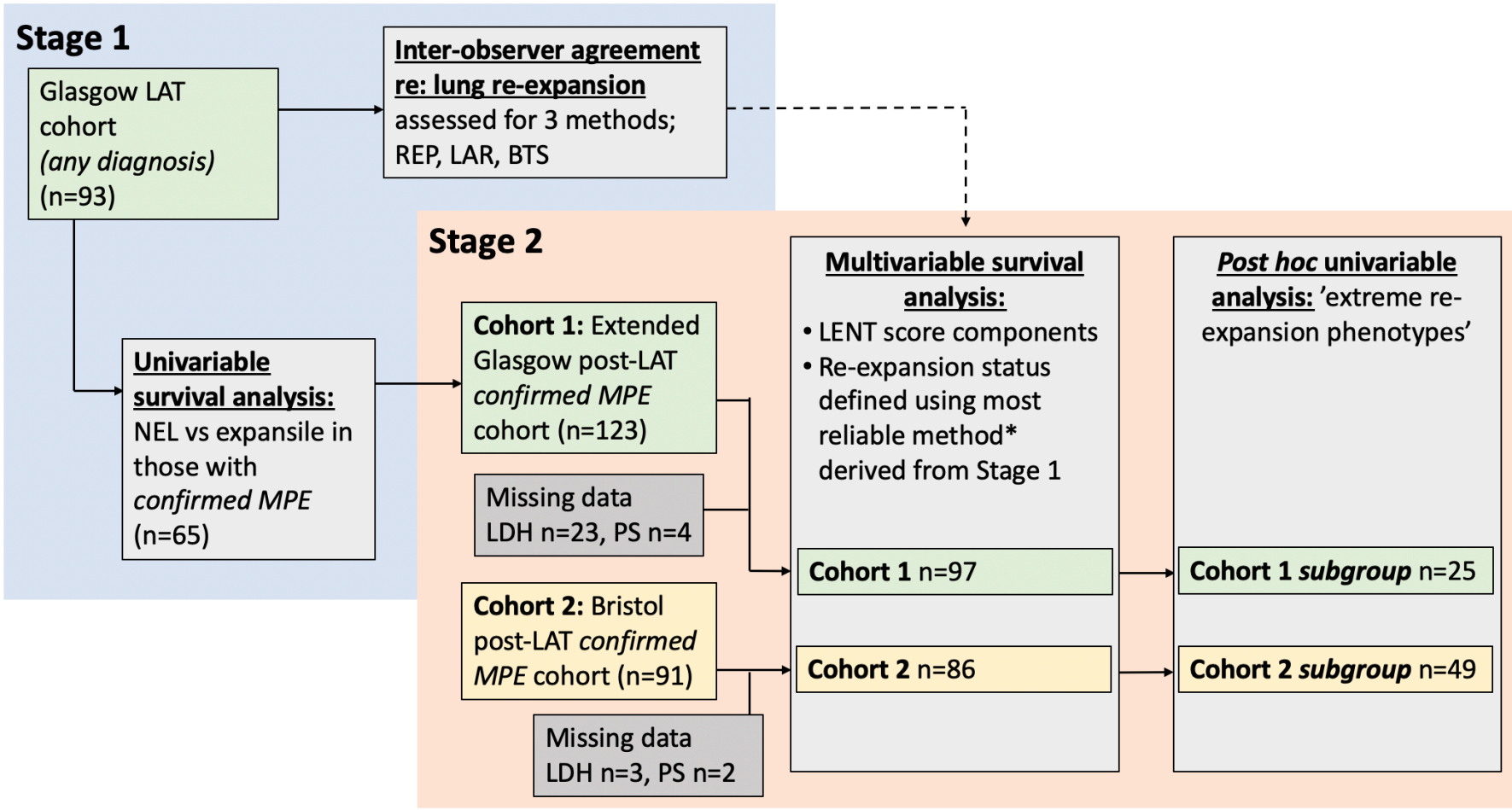


Figure 3.1 Flowchart summarising study sequence and patient numbers included

LAT, local anaesthetic thoracoscopy; NEL, non-expansile lung; MPE, malignant pleural effusion; REP, re-expansion proportion; LAR, lateral apposition ratio; BTS, British Thoracic Society; LDH, lactate dehydrogenase; PS, performance status. *highest Kappa statistic

Table 3.1 Patient demographics and final pleural diagnosis in a single centre cohort (n=93) who underwent diagnostic LAT (Stage 1)

Age, mean (95% CI)	73 (71 – 75)
Male, n (%)	72 (77)
Right sided, n (%)	46 (49%)
Final pleural diagnosis, n (%)	
Malignant:	
Mesothelioma	33
Lung	16
Breast	9
Other	7
Benign:	
BAPE	13
Other	9
Diagnosis uncertain	6
NEL, n (%)	18 (19)

BAPE, benign asbestos pleural effusion; NEL, non-expansile lung

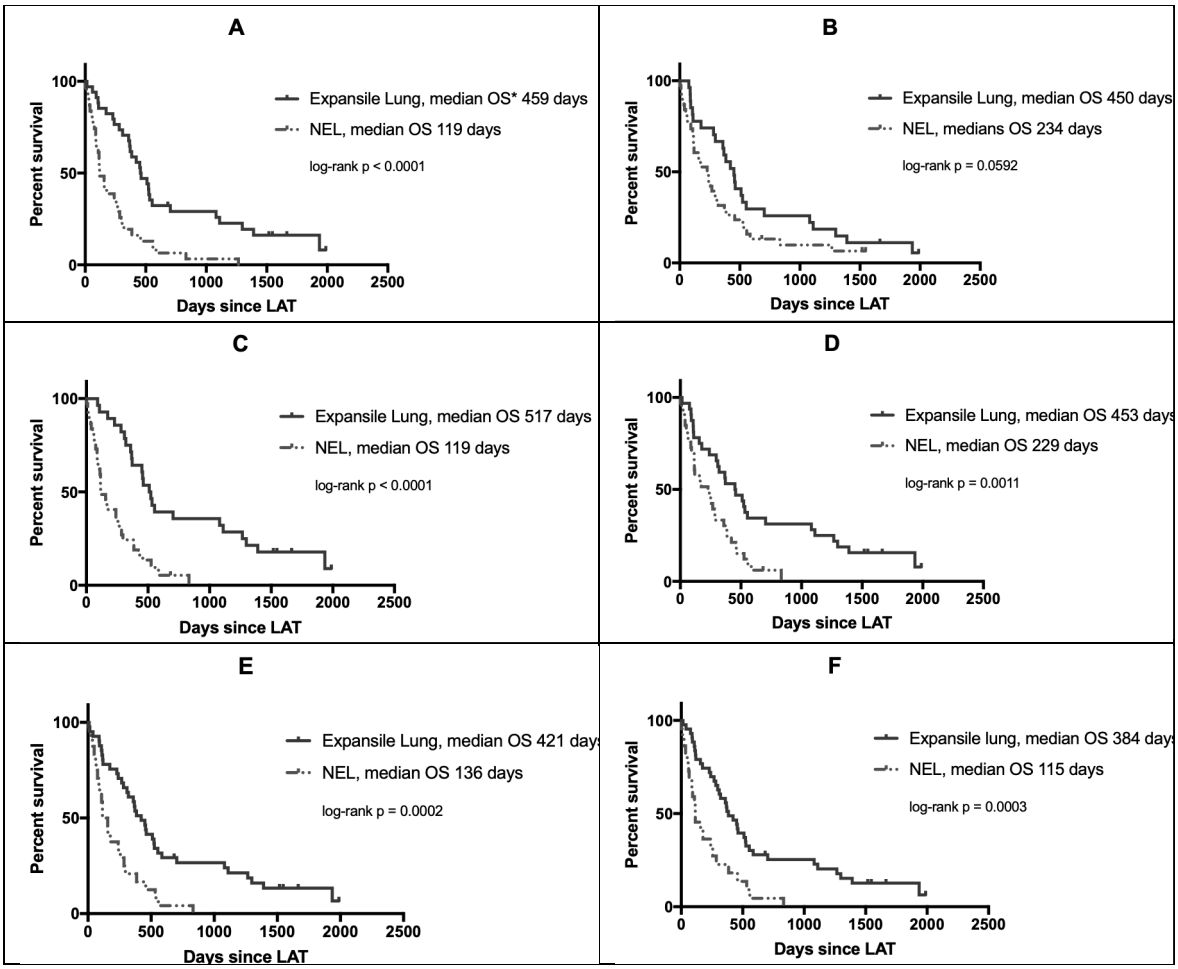


Figure 3.2 Kaplan-Meier plots illustrating survival stratified by presence or absence of NEL for each operator and method of CXR analysis in 65 patients with confirmed MPE (Stage 1). A – Primary assessor (GAM) using Re-expansion Proportion (REP), B – Secondary assessor (ACK) using REP, C – GAM using Lateral Apposition Ratio (LAR), D – ACK using LAR, E – GAM using BTS method (BTS), F – ACK using BTS.

OS, overall survival

3.3.2 Prognostic significance of NEL: multivariable analysis (Stage 2)

3.3.2.1 Study population

214 eligible patients were identified. Complete data were available for 183/214 (86%: Cohort 1 n=97, Cohort 2 n=86); cases with any missing data were excluded (Cohort 1: 23 LDH, 4 PS; Cohort 2: 3 LDH, 2 PS). Demographics and clinical data were broadly similar between cohorts (Table 3.2). However, more patients in Cohort 2 were male and had a diagnosis of MPM, and more patients were in PS group 2.

Table 3.2 Patient demographics, clinical characteristics and median overall survival in two independent MPE cohorts who underwent diagnostic LAT (Stage 2)

	Cohort 1 (n=97)	**Cohort 2 (n=86)**	**p**
Age, mean (95% CI)	71 (69 - 74)	72 (70 - 75)	0.581
Male, n (%)	65 (67)	69 (80)	**0.047**
Right sided, n (%)	56 (58)	44 (51)	0.457
Tumour type, n (%)			
Mesothelioma	56 (58)	64 (74)	**0.012**
Lung	21 (22)	10 (12)	0.079
Breast	6 (6)	5 (6)	0.999
Genitourinary	5 (5)	2 (2)	0.450
Gastrointestinal	3 (3)	3 (3)	0.999
Haematological	1 (1)	0 (0)	0.999
Other	5 (5)	2 (2)	0.450
Performance status, n (%)			
0	18 (19)	14 (16)	0.702
1	64 (66)	53 (62)	0.643
2	9 (9)	16 (19)	0.085
3	6 (6)	3 (3)	0.504
NLR, median (IQR)	4.2 (2.8 - 5.9)	4.16 (2.79 - 5.29)	0.878
LDH, median IU/mL (IQR)	0.36 (0.21 - 0.63)	0.52 (0.35 - 0.79)	**0.003**
Total LENT score, median (IQR)	1 (1 - 3)	1.5 (1 - 2)	0.534
Median overall survival, days (IQR)	267 (116 - 525)	360 (172 - 537)	0.122
NEL, n (%)	33 (34)	15 (17)	**0.012**

IQR, interquartile range; CI, confidence interval; CUP, carcinoma of unknown primary; SCC, squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; LDH, pleural fluid lactate dehydrogenase; NEL, non-expansile lung.

3.3.2.2 Lung re-expansion and inter-observer agreement

Maximal lung re-expansion was observed within 24 hours of LAT in 53/97 (55%) in Cohort 1 and 53/86 (62%) in Cohort 2. The prevalence of NEL, based on the radiographic classification made by the primary assessor at each site, was 34% (33/97) in Cohort 1 and 17% (15/86) in Cohort 2. However, inter-observer agreement between assessors at each site regarding NEL was only fair-to-moderate [89] (Cohort 1 κ 0.38 (95% CI:0.21–0.55); Cohort 2 κ 0.51 (95% CI:0.30–0.72)).

3.3.2.3 Prognostic impact of NEL

Patients with NEL, as defined by the primary assessor, had shorter median OS than patients without NEL in both cohorts (Figure 3.3). In Cohort 1, NEL defined in this manner, was independently associated with adverse survival (HR 2.19, 95% CI:1.31–3.66), but this was not replicated in Cohort 2 (HR 1.42, 95% CI:0.71–2.87 – Table 3.3). However, in a subsequent *post hoc* analysis, median OS was significantly shorter in both cohorts in cases with Complete NEL (Cohort 1, 6/97 (6%); Cohort 2, 5/86 (6%)) compared to those with Complete Expansion (Cohort 1, 19/97 (20%); Cohort 2, 44/86 (51%)), see Figure 3.4. Figure 3.5 shows examples of CXRs classified by the primary assessor in Cohort 1 as a) NEL on the basis of <50% pleural apposition for the primary outcome, and examples of extreme re-expansion phenotypes used in the *post hoc* analysis: b) Complete NEL and c) Complete Expansion.

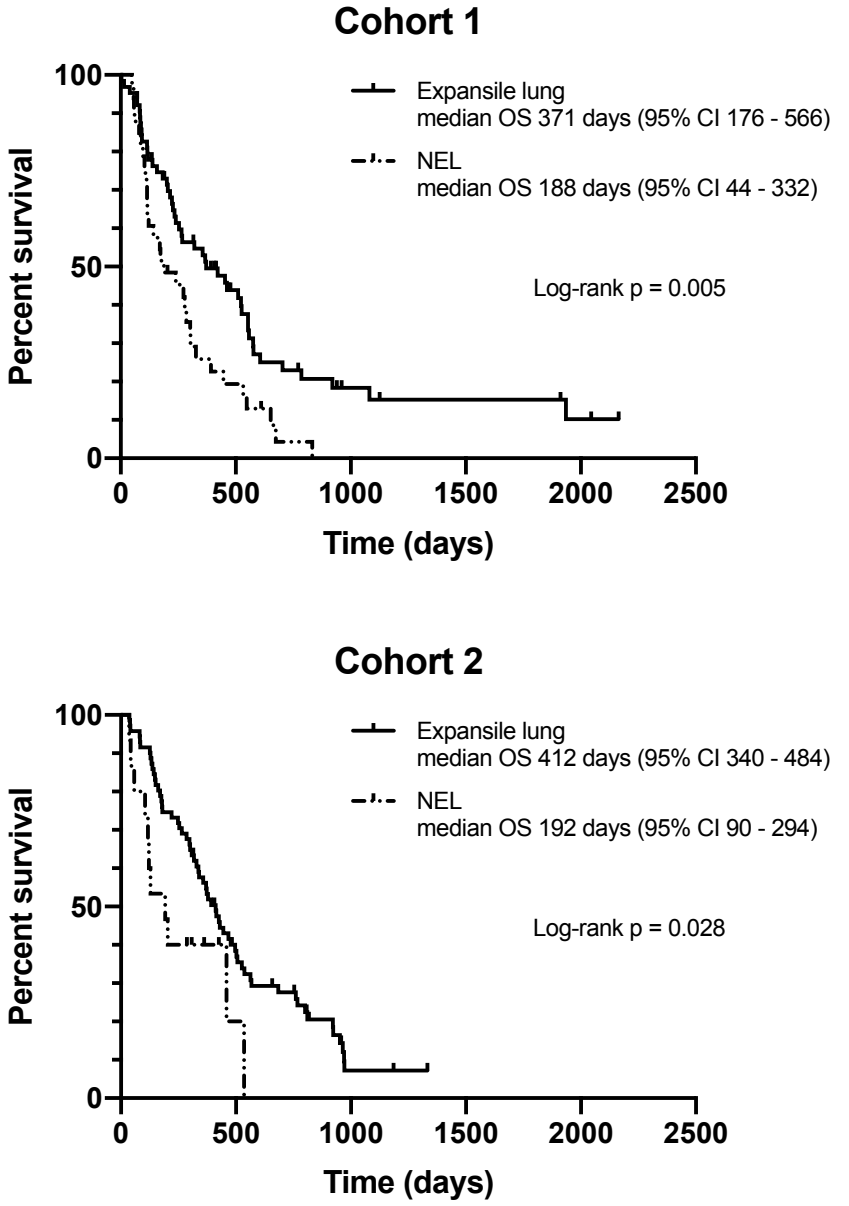


Figure 3.3 OS stratified by lung re-expansion status (Expansile lung vs NEL) following LAT in 2 cohorts of patients with MPE (Cohort 1 n=97, Cohort 2 n=86)

Table 3.3 Results of univariable and multivariable Cox regression analysis in two MPE cohorts. Multivariable model outputs report the association between predictors of overall survival (OS), including NEL and individual components of the LENT prognostic score. Predictors independently associated with OS are highlighted in bold.

	Univariable analysis		**Multivariable analysis**	
	HR (95% CI)	**p**	**HR (95% CI)**	**p**
COHORT 1 (n=97)				
NEL	**1.93 (1.21 – 3.06)**	**0.006**	**2.19 (1.31 – 3.66)**	**0.003**
LENT tumour score*	**1.69 (1.31 – 2.19)**	**0.000**	**1.65 (1.24 – 2.19)**	**0.001**
Pleural fluid LDH (IU/mL)	**1.29 (1.09 – 1.54)**	**0.004**	**1.25 (1.03 – 1.52)**	**0.025**
NLR	**1.12 (1.04 – 1.21)**	**0.004**	**1.09 (1.01 – 1.18)**	**0.026**
ECOG PS	**1.93 (1.40 – 2.67)**	**0.000**	1.27 (0.88 – 1.85)	0.206
COHORT 2 (n=86)				
NEL	**2.08 (1.07 – 4.04)**	**0.032**	1.42 (0.71 – 2.87)	0.322
LENT tumour score*	**1.78 (1.32 – 2.38)**	**0.000**	**2.24 (1.60 – 3.15)**	**0.000**
Pleural fluid LDH (IU/mL)	**2.04 (1.37 – 3.05)**	**0.000**	**2.34 (1.50 – 3.64)**	**0.000**
NLR	1.00 (0.93 – 1.07)	0.916	0.95 (0.88 – 1.02)	0.173
ECOG PS	1.26 (0.90 – 1.75)	0.184	1.27 (0.88 – 1.84)	0.197

HR, hazard ratio; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NLR, neutrophil-to-lymphocyte ratio; LDH, lactate dehydrogenase; IU/mL, International Units/millilitre; NEL, non-expansile lung. * Tumour-type risk score used in 'LENT' prognostic scoring system: mesothelioma or lymphoma = 0; breast, ovarian or renal cancer = 1; lung or other tumour-type

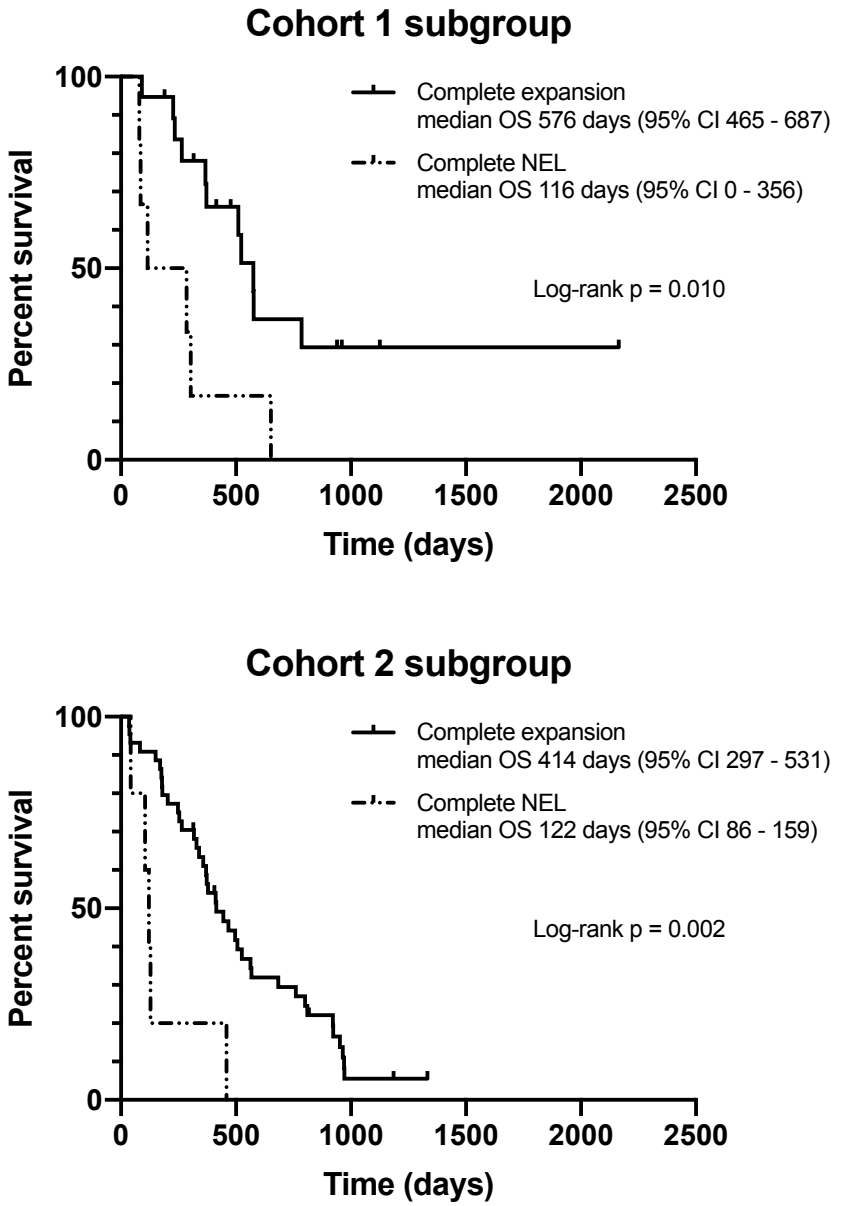


Figure 3.4 Overall Survival stratified by extreme expansion phenotypes (Complete NEL vs Complete Expansion) following LAT in a post hoc analysis of subgroups of Cohort 1 (n=25) and Cohort 2 (n=49)

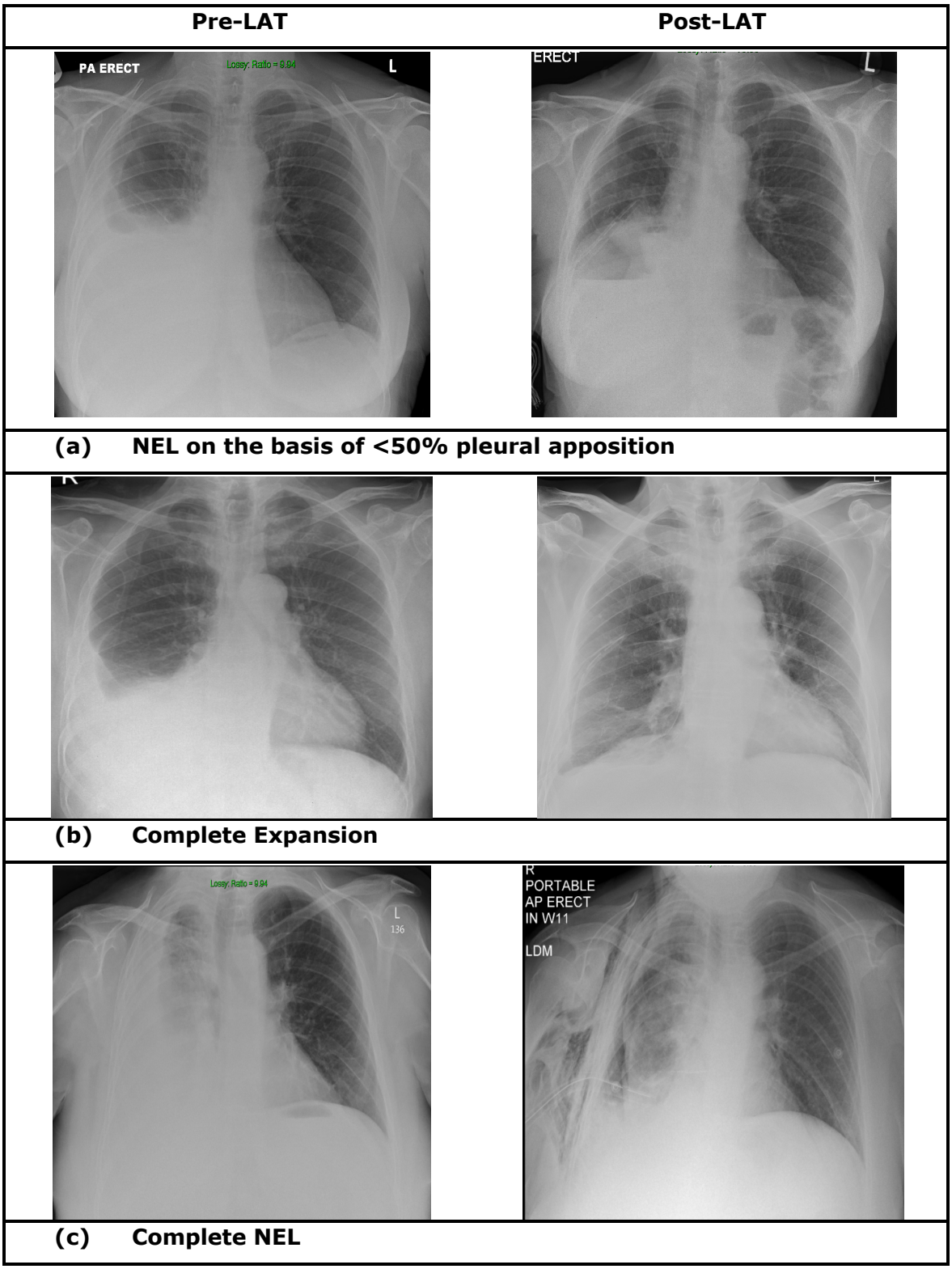


Figure 3.5 Examples of lung re-expansion classification based on subjective visual estimation before and after complete malignant pleural effusion drainage at Local Anaesthetic Thoracoscopy (LAT): (a) NEL on basis of <50% pleural apposition, (b) Complete expansion (c) Complete NEL

3.4 Discussion

3.4.1 Optimal radiographic identification of post-drainage NEL

In Stage 1 of this retrospective cohort study, poor agreement was identified between assessors for 2 semi-objective definitions of NEL, based on the pre-discharge chest radiograph following LAT, and only moderate inter-observer agreement using the subjective BTS method. Based on the primary assessor's data, the BTS method demonstrated a high degree of sensitivity and specificity in the prediction of a subsequent expert diagnosis of NEL. This finding was unsurprising as it is likely that the expert assessor was heavily influenced by the BTS guideline statement concerning NEL (see further discussion in Section 3.4.5). The semi-objective definitions of NEL (REP and LAR) performed poorly in this regard.

3.4.1.1 BTS definition

This definition of NEL was based on guidance made in the 2010 BTS Pleural Guideline, which advises that pleurodesis is unlikely to be successful in cases with clear evidence of NEL, as defined by <50% pleural apposition. [4] The level of agreement between clinicians in Stage 2 (κ <0.5 for both cohorts) was significantly lower than observed in Stage 1 (κ 0.68). The reasons for this sizable difference in agreement between stages of the study are unclear. However, the discrepancy may reflect the challenge of judging pleural contact in malignant cases (comprising 70% of the cohort in Stage 1 vs 100% in Stage 2), due to the presence of bulky pleural metastases or malignant pleural thickening which may mimic residual pleural fluid.

3.4.1.2 Re-expansion proportion

The REP technique is likely to have been limited by large variations in delineating the hemidiaphragm position and lower limit of lung re-expansion where significant residual pleural fluid remained. In the MIST-2 study, on which the REP method is based, all measured regions of interest (ROIs) varied by less than 5%. [85] In contrast, our REP data varied by up to 39% with a mean difference between assessors of 8%. There may be several reasons for this difference, including the involvement of expert thoracic radiologists in the MIST-2 study measurements. Although ultimately not required during the conduct of the trial, the MIST-2 protocol also mandated a joint review of ROIs if significant

inter-observer variation was observed, allowing a final, jointly agreed ROI to be defined. While application of a similar approach to the current study may have minimized variance and potentially improved the predictive performance of the REP method, it would not reflect clinical practice and therefore be of limited generalisability. These findings suggest that the REP method is subject to considerable variation when routinely applied by respiratory clinicians.

3.4.1.3 Lateral apposition ratio

The LAR approach makes approximation of the ipsilateral costophrenic angle more consistent between observers, which perhaps accounts for the slight improvement in inter-observer agreement once measurements were dichotomised. However, the raw continuous LAR measurements demonstrate large variation between assessors. It appears likely that this relates to considerable difficulty in reliably differentiating between pleural thickening, tumour deposits and non-dependent fluid in cases with residual pleural opacification. This particular challenge may be overcome through use of systematic thoracic ultrasound (TUS), which is capable of reliably differentiating between these and identifying clear sites of 'lung sliding', and therefore certain pleural apposition. This technique is currently under evaluation in the randomised SIMPLE trial (ISRCTN16441661). [58]

3.4.2 Prevalence of NEL

NEL following complete drainage of MPE at LAT was relatively common (Stage 2; Cohort 1 34%, Cohort 2 17%). However, it is difficult to compare these data to the existing MPE literature since the definition of NEL used in earlier studies varies widely. In the AMPLE trial, [3] which compared TSP with IPC management, NEL was defined pragmatically as 'incomplete lung expansion', and was reported in only 3% (5/146) participants. In contrast, 32% (28/87) patients had NEL in AMPLE-2, [35] which compared different IPC drainage strategies, based on a definition of <75% lateral apposition. Other studies report rates that lie between these extremes, possibly reflecting different definitions and/or exclusion criteria, e.g. 6% in TIME2 (based on <50% pleural apposition), [2] 13% in IPC-PLUS (based on <75% pleural apposition), [48] and 29% in the Phase III Intergroup Study (based on <90% expansion). [5]

3.4.3 Prognostic impact of NEL in MPE

In Stage 1, all measures of NEL were strongly and consistently associated with a 2-4-fold reduction in median survival in a single centre cohort of patients with confirmed MPE. This effect was seen using all methods by all observers, with the greatest mortality risk associated with low LAR results. This finding was confirmed using the most reproducible definition (BTS) in 2 independent cohorts in Stage 2 of the study. In this analysis, NEL was independently associated with adverse survival in Cohort 1 (HR for death 2.19, 95% CI:1.31–3.66, p=0.003), but this was not replicated in Cohort 2, in which the HR for death crossed 1 (HR 1.42, 95% CI:0.71–2.87, p=0.322). This may reflect the smaller number of NEL cases in that series (17% (15/86) vs 34% (33/97)), with an attendant reduction in statistical power and a type II error. Clearly, it is also possible that this failure to validate means the survival effect observed in Cohort 1 is not externally valid, i.e. that NEL is not generally associated with adverse survival in MPE patients. However, it is likely that the variability also reported in classifying NEL radiographically may contribute to borderline cases being incorrectly classified and potentially confounded survival estimates in these cases. This possibility prompted a *post hoc* analysis based on 'extreme expansion' phenotypes since there is no real risk of misclassification in these cases. This analysis, which demonstrated significantly inferior survival in cases with 'Complete NEL' vs those with 'Complete Expansion' in both cohorts supports the assertion that the prognostic effect of NEL identified is genuine.

3.4.3.1 Previous studies relating NEL to survival

In an earlier retrospective study, Leemans et al reported similar adverse survival (median OS 66 days vs 169 days) in patients with MPE (due to a range of tumour types) who failed thoracoscopic talc pleurodesis due to NEL. [90] In malignant pleural mesothelioma (MPM), visceral pleural tumour, a frequent cause of NEL, has historically been associated with adverse survival. [91] More recently, Bibby et al confirmed this association based on radiographic NEL. In that study the HR for death was 1.80 (95% CI:1.16–2.80)) in 192 patients with MPM, 64 of whom (33%) developed NEL at some point during their disease course. [86] The use of serial chest radiographs over a long follow-up period and inclusion of only MPM in this study differs from the work presented in this thesis but the observation of excess mortality is concordant with the conclusions presented.

3.4.3.2 Potential mechanisms

The most intuitive potential explanation for this prognostic finding is that NEL is simply associated with more advanced disease; i.e. a thicker concentric pleural tumour rind or bulkier proximal disease leading to airway obstruction. It was beyond the scope of the current study to explore such mechanisms as its retrospective nature precluded the collection of sufficiently detailed anatomical and staging information. However, it is noteworthy that in patients with MPM, Bibby et al recently reported that adverse survival associated with NEL was independent of disease stage, and that NEL was more common in early stage disease. [86] Accepting the limitations of staging in MPM, their data suggests less obvious biological mechanisms are likely to be implicated, at least in patients with malignant effusion associated with MPM. Given the heterogenous nature of the cohorts studied here, several alternative mechanisms are likely to be implicated. Physiological compromise or additional pleural procedures/hospitalisation associated with NEL may also be relevant. A larger study would be required to assess these important questions.

3.4.4 Clinical significance

Radiographic interpretation is a cornerstone in the management of patients with MPE. In patients undergoing fluid drainage, CXR findings directly determine the timing of talc slurry instillation and chest drain removal. [4] As such, variation in CXR interpretation regarding lung re-expansion (and the presence of NEL) is of critical importance and could result in futile talc slurry instillation and inappropriate prolongation of hospitalisation if NEL is under-recognised. Conversely, such variation may also result in missed opportunities to deliver talc pleurodesis and lasting symptom control if expansile lung is mis-classified as NEL. Although data relating a particular CXR definition to subsequent TSP success do not exist, the findings described in this thesis of only fair-to-moderate inter-observer agreement support the use of consensus judgments regarding lung re-expansion rather than relying on a single assessor. In particular, this approach should be considered in clinical trial design where patients may be excluded from enrolment or study procedures based on a single observer's judgement. [84]

The level of disagreement reported here highlights the challenges involved in radiographic NEL assessment, even when experienced assessors are involved. Development of a reliable method of NEL detection should therefore be a clinical imperative. Evaluation of 3-dimensional lung expansion based on a 2-dimensional image is an inherently flawed concept and a technique which provides a global assessment of the pleural cavity is clearly required. As described in the introduction to this thesis, a range of potential techniques to address this challenge are under investigation. With particular reference to post-drainage NEL identification, two UK multicentre studies are currently indirectly evaluating the potential utility of systematic multiplanar thoracic ultrasound scanning to detect post-drainage NEL. [58,59] Future research of novel NEL detection methods should also seek to establish the relationships between varying expansion thresholds and clinical outcomes. However, as previously discussed, a robust method to identify NEL prior to attempting complete pleural drainage would appear to offer the greatest potential benefit to patients. Possible methods of pre-drainage NEL detection are discussed further in Chapter 4.

3.4.5 Study limitations

Both stages of this study were limited by their retrospective designs. Consequently, missing data was inevitable, and the statistical power of the study was inherently constrained. Patient numbers also precluded sub-group analyses and exploration of a potential interaction between MPM disease stage, NEL and mortality, which is entirely plausible based on previous research. [91]

In Stage 1, subjective expert judgment was used to define a ‘gold standard’ for NEL to allow the predictive performance of each method to be established. This was likely to have been heavily influenced by the use of the BTS method, therefore biasing the predictive performance results in favour of that approach. However, the expert judgement was not exclusively based on the BTS method of radiographic assessment; it also integrated all available imaging (CT and US) and clinical acumen. It was therefore justified as a pragmatic tool to allow optimal cut-points for REP and LAR to be established, and, in turn, dichotomise the data for direct comparison with the BTS method.

Due to reliance on LAT databases, and its geographical basis in post-industrial coastal cities, this study included a higher proportion of patients with MPM than is encountered in routine practice in other areas. Since the natural course of MPM is to readily proliferate from parietal to visceral pleura surfaces, the generalisability of our prognostic findings to a more heterogeneous MPE cohort should not be assumed. Additionally, in most centres, the majority of patients with symptomatic MPE will be managed by closed pleural drainage via ICD or IPC rather than open drainage at LAT. However, expansion outcomes are unlikely to vary meaningfully between closed drainage and LAT since neither decortication nor any significant division of adhesions is undertaken during the latter.

Finally, it is important to note that the guideline statement used to derive the 'BTS' NEL definition used here was not designed to be a precise diagnostic criterion and other studies have used alternatives (e.g. <75% pleural apposition). [35,48,86] An alternative definition of NEL might improve inter-observer variability, but may be less clinically relevant since subtle NEL might still be amenable to a pleurodesis attempt. Addressing this question was beyond the scope of the current study.

3.4.6 Conclusions

NEL following drainage of MPE at LAT is a common finding (17–34%). A similar prevalence of underlying NEL might be expected in a generalised population of patients with MPE but cannot be assumed. Accepting this limitation, NEL appears to be under-represented in significant trials of MPE management (e.g. TIME-2 and AMPLE). [2,3]

Radiographic identification of NEL is subject to a high level of inter-observer variation. NEL is associated with adverse survival, although the independence of this relationship was not externally validated in this work, probably due to an inadequate sample size. These findings should be considered in clinical decision-making and MPE trial design, particularly when single observers are used. Future research should seek to identify clinically deployable biomarkers for NEL that are associated with less inter-observer variation. An ideal biomarker would reliably detect underlying NEL prior to committing patients to complete effusion drainage. This concept is explored further in Chapter 4.

Chapter 4

FEASIBILITY OF A RANDOMISED CONTROLLED TRIAL OF ELASTANCE-DIRECTED MANAGEMENT IN MALIGNANT PLEURAL EFFUSION

4 Chapter 4: Feasibility of a randomised controlled trial of elastance-directed management in malignant pleural effusion

4.1 Introduction

This chapter describes the pre-EDIT trial; a prospective feasibility RCT of a pleural elastance (P_{EL})-directed treatment pathway (EDIT management) in patients with symptomatic MPE. [92] Pre-EDIT was designed to assess the feasibility of delivering, and inform the design of, a potential future randomised Phase III RCT testing the efficacy of EDIT management compared to inpatient TSP as a standard of care.

The feasibility of this study design is described in this chapter in terms of patient recruitment, the technical deliverability of EDIT management, and limitations of this approach, including a description of adverse events encountered. The background to this trial and rationale for its design is first reiterated.

4.1.1 Current treatment of symptomatic malignant pleural effusion

As previously discussed, MPE frequently leads to disabling breathlessness which may be definitively managed by either day case insertion of an IPC to facilitate regular domiciliary drainage, or TSP during a 4-7 day hospital admission. [46,47] Inpatient TSP provides long-term symptom control in 71-78% of patients, [3,5] and avoids the inconvenience and risks (notably pleural infection) associated with IPC drainage. [31] However, MPE associated with underlying NEL is not amenable to successful TSP and is most appropriately managed with IPC insertion. [4] Since reliable pre-drainage detection of NEL is not feasible within existing pathways, clinically occult NEL is a frequent cause of TSP failure.

Universal IPC-based management has been suggested as a solution to overcome this unpredictability, particularly since the delivery of talc via IPC has been shown to improve pleurodesis rates if the lung re-expands. [93] However, this strategy still requires IPC placement, which is unattractive to a significant proportion of patients [43] and associated with higher healthcare costs in

patients who require prolonged drainage beyond 14 weeks. [40,41] It is also important to note that ambulatory TSP delivers a pleurodesis success rate that is significantly inferior (51% at 10 weeks) [93] to that associated with inpatient TSP, albeit based on non-comparative data.

4.1.2 An optimal MPE treatment pathway

A logical refinement to MPE management would therefore be the development of a treatment pathway which makes the best use of the relative advantages and disadvantages of TSP and IPC drainage. An early assessment of lung re-expansion potential might allow clinicians to deliver TSP with greater confidence of success by excluding patients with NEL and instead directing these individuals towards a first-line IPC. This concept is particularly important because, as detailed in Chapter 3 (Section 3.4.2), NEL is almost certainly under-represented in the evidence base underpinning current MPE management (6% NEL in TIME2, 3% NEL in AMPLE), [2,3] and clinical equipoise between IPC insertion and TSP as first-line definitive interventions cannot be assumed.

4.1.3 Pre-drainage detection of NEL

Pleural elastance (P_{EL}) and atelectatic lung excursion/strain related to cardiac impulse have previously been reported as biomarkers of NEL. [50,61,67,71,94,95] The former is an intrinsic property of the pleural space derived from pleural manometry data recorded during thoracentesis, while the latter may be assessed using either motion-mode (M-mode) and speckle tracking ultrasonography. These techniques are discussed in detail in the Introduction to this thesis (Section 1.6 and Section 1.5.4.3).

For pre-drainage detection of NEL, I chose to focus on assessment of P_{EL} over ultrasound methods based on an interest in our unit in this area, a larger body of preceding research and a judgement that there was greater scope to optimise the technique (see Section 4.1.3.2 below), and integrate it into a single intervention procedure in a future definitive trial. However, given its widespread availability, I also included M-mode sonography as a subsidiary end-point in pre-EDIT. The validity of these design choices were explored in a number of subsidiary analyses within the pre-EDIT trial and the results of these analyses are presented separately in Chapter 5. I intentionally did not

incorporate ultrasound strain assessment, which I judged to be inherently unsuitable for use in routine clinical practice due a requirement for specialist equipment and operator training.

Previously published data regarding P_{EL} in the detection NEL has already been summarised in the Introduction (section 1.6.7). In the following sections the rationale used to define the P_{EL} threshold and measurement methodology used in pre-EDIT has been summarised.

4.1.4 Pleural elastance as a NEL biomarker

P_{EL} is a well-recognised physiological metric that has been studied extensively in observational settings. It is defined as the intrapleural pressure (IPP) change divided by the volume of pleural cavity volume change during thoracentesis, which is generally assumed to be equal to the volume of pleural fluid aspirated. Characteristic patterns of IPP change during thoracentesis, associated with expansile lung and NEL (subdivided into 'entrapped' and 'trapped' lung), are described in Introduction section 1.6.4. However, to date, only one study by Lan *et al* has identified an association between P_{EL} and pleurodesis success, defined in that study as elimination of the requirement for further therapeutic thoracentesis to alleviate symptoms at 1-month post-pleurodesis. [67] Lan *et al* reported that point estimates of $P_{EL} \geq 19$ cmH_2O/L over an aspiration volume of 500ml were associated with radiographic NEL with a sensitivity of 79% (95% confidence interval (CI) 49-94%) and specificity of 94% (95% CI 83-99%). Using the same P_{EL} threshold, subsequent pleurodesis success was predicted with a sensitivity of 75% (95% CI 22-99%) and a specificity of 100%. The sensitivity of this approach is clearly only moderate, and is likely to have been limited by a P_{EL} threshold significantly above the upper limit of normal, which was subsequently defined as 14.5 cmH_2O/L, [13] and the small aspiration volume used (500ml), which is likely to have been inadequate to detect all cases of biphasic NEL (see section 1.6.4).

4.1.5 Choice of P_{EL} threshold in pre-EDIT

As described in Section 1.8.3, use of a lower P_{EL} threshold than Lan *et al* (19 cmH_2O/L) and measurement over a larger total aspiration volume would be expected to increase the sensitivity of NEL detection, but could potentially

sacrifice specificity, particularly if IPP rises transiently due to coughing, an inadvertent Valsalva manoeuvre or unknown measurement artefacts. Therefore, in pre-EDIT, a lower P_{EL} threshold was used (14.5 rather than 19 cmH_2O/L) over the course of a large volume aspiration, but we decided that this would only be met if it was sustained over at least 250ml of fluid removed. This required definition of an entirely novel definition based on a rolling average of P_{EL} recording over the preceding 250ml fluid removed (termed P_{EL250}). In pre-EDIT, aspiration volume was limited only by the development of symptoms (chest discomfort or excessive coughing), a drop in IPP below previously reported safety thresholds, or a target pleural effusion depth (designed to retain sufficient residual fluid to facilitate a safe definitive intervention on the same day). NEL was therefore defined by a maximum $P_{EL250} \geq 14.5$ cm H_2O/L occurring at any point during large volume aspiration. This definition aimed to detect NEL at the earliest possible opportunity with a high degree of sensitivity while preserving specificity.

4.1.6 Technical considerations in IPP measurement

Previous pleural manometry equipment has been hampered by technical limitations, largely relating to poor damping of pressure variations related to normal respiration and/or the need for cumbersome improvised equipment. During the work presented in this thesis, a purpose-built, single-use, CE-marked digital pleural manometry (DPM) catheter was developed in conjunction with Rocket Medical (UK) which allows continuous IPP measurement during thoracentesis. The device measures IPP once per second and is mechanically damped via the narrow independent lumen linking the pleural cavity to the electronic transducer. IPP is also temporally damped as the equipment displays a mean IPP on a re-usable digital display unit, based on the preceding 5 seconds of data recorded. The precision and accuracy of the electronic transducer within the manometry system was laboratory tested by Rocket Medical (UK) during product development and found to read within +/- 5% of a calibrated laboratory device at simulated pressures between +20 cmH_2O and -30 cmH_2O. The manometer was electromagnetic compatibility tested and passed BS EN 60601-1-2:2015 and BS EN 60601-1:2006+A1:2013.

4.1.7 Delivery of P_{EL}-directed management and safety considerations

By definition, the EDIT pathway requires a large volume thoracentesis procedure prior to allocation to TSP or IPC. If the allocated procedure cannot be delivered promptly, and ideally at the same sitting, any pathway efficiency gained through the detection of NEL is lost. However, placement any form of Seldinger drain may be technically challenging after removal of the majority of the effusion during P_{EL} assessment. Therefore, within the EDIT protocol, a target aspiration volume was included as a stop criterion during aspiration. The method of assessing this target volume evolved during the conduct of the trial and is discussed further in Chapter 5. The protocol also allowed that, if required, a 'Boutin-type' needle could be employed for pneumothorax induction to ensure safe placement of P_{EL}-allocated IPC or TP. This is regularly practiced at level II thoracoscopy centres when no, or minimal, pleural fluid is present at LAT. [7] A 2mm diameter 'Boutin-type' pleural access needle without biopsy side gate (Novatech SA (France)) was deliberately chosen for this purpose over a more conventional 3mm Boutin trocar in order to avoid inadvertent tissue damage from an open biopsy gate during trocar removal (see Figure 4.1). In normal use, the Boutin biopsy gate would be safely occluded by the internal stylet prior to removal, however within pre-EDIT the trocar would potentially be used to pass a thin Seldinger guidewire into the pleural space thus precluding stylet replacement. It was also acknowledged in the development of the study that if a regular requirement for pneumothorax induction was identified, there would clearly be implications for the feasibility of any subsequent multi-centre Phase III trial, and any subsequent clinical deployment.

Figure 4.1 Single-use pleural access needles © Novatech SA (France). A – 2mm diameter 'Boutin-type' needle without biopsy side gate used in pre-EDIT. B - Conventional 3mm diameter Boutin pleural trocar showing cutting biopsy side gate. Both needle designs have a working length of 78mm and are equipped with a sharp and a blunt stylet.

4.1.8 Treatment Preferences Survey

Limited data exists regarding the factors most important to patients when weighing up their management options for MPE. Qualitative data from the Oxford pleural group indicate that in a sample of 18 patients who underwent inpatient TSP for symptomatic MPE, over half indicated that they would not consider IPC management. [43] Furthermore, 12/15 (80%) survey respondents who underwent inpatient TSP believed outpatient management would have either no effect or a negative effect on their quality of life. However, in contrast, 7/8 (88%) who underwent IPC drainage rated the experience as positive. Further research is therefore clearly needed to better appreciate the heterogeneous range of patient preconceptions and treatment priorities, and thus inform the design of future MPE therapeutic trials. During the conduct of pre-EDIT, the opportunity was taken to gather additional semi-qualitative data on patient decision-making around MPE management using a Treatment Preferences Survey (TPS). The findings from this survey are presented in Chapter 5.

4.2 Materials and methods

A full description of the pre-EDIT study design is provided in Chapter 2, Section 2.4 and in a published open-access trial protocol paper. A brief summary is provided in this section. [92]

4.2.1 Trial Design

Pre-EDIT was a single centre, randomised, controlled, open-label feasibility trial. The design is summarised in Chapter 2, section 2.4.6 (Figure 2.7).

4.2.2 Trial Objectives and Outcome Measures

The primary objective was to determine whether sufficient numbers could be recruited and randomised for a future multi-centre Phase III trial to be considered feasible. Feasibility was defined *a priori* as the recruitment and randomisation of 30 patients over 12 months (or 15 patients over any 6-month period). The primary outcome measure was recruitment rate. Secondary objectives and associated outcome measures addressing important safety and practicality issues are shown in Chapter 2, Table 2.2. Additional secondary and exploratory objectives related to volumetric Magnetic Resonance Imaging (MRI) validation of the current definition of P_{EL}, and the embedded patient TPS, are described in Chapter 5 of this thesis. A *post hoc* analysis was also performed regarding the sensitivity and specificity of high P_{EL} for radiographic NEL; defined here as NEL_{50} (see section 2.4.16).

4.2.3 Screening, Enrolment and Randomization

Eligibility criteria are shown in Chapter 2, Section 2.4.3. All potentially eligible patients were pre-screened at the QEUH using electronic records. Those without obvious exclusion criteria were invited to a formal screening visit. Specific written consent to screening was taken. Patients meeting all eligibility criteria after screening provided further written consent before enrolment and were randomly allocated 1:1 between EDIT management and Standard Care (TSP).

4.2.4 Trial Interventions

Study interventions, according to group allocation, were performed at the QEUH within 72 hours of randomisation.

4.2.4.1 Standard Care

Standard Care involved placement of a 12F intercostal chest drain (ICD), complete drainage +/- attempted TSP in patients demonstrating ≥50% pleural re-apposition on post-drainage CXR. [4]

4.2.4.2 EDIT management

EDIT management was a 3-step process. Step 1 involved P_{EL} assessment during a large volume pleural fluid aspiration using the bespoke DPM catheter (Rocket Medical (UK)). IPP was recorded at 50ml intervals until any of the following: chest discomfort or excessive coughing; IPP ≤-20cmH_2O; horizontal pleural cavity width ≤30mm adjacent to catheter on ultrasound. No volume limit for fluid aspiration was used. The second step involved computation of the maximum sustained P_{EL} and unbiased allocation to an attempt at TSP or IPC placement. This is discussed in detail in Chapter 2, Section 2.4.11.3. The final step involved delivery of elastance-directed pleural management within 24 hours. Patients with *normal* P_{EL}, defined as $MaxP_{EL250}$ < 14.5 cmH_2O/L at all points, underwent 12F ICD placement with a view subsequent inpatient TSP. Patients with *high* P_{EL}, defined as $MaxP_{EL250}$ ≥ 14.5 cmH_2O/L at any point, underwent IPC placement.

4.2.5 Follow-up

In addition to routine clinical follow-up (approximately 14-, 30- and 60-days post-discharge), a single trial follow-up visit at 90 days (+/-10) was arranged. A CXR was acquired and details of hospital admissions, repeat pleural interventions, and clinic visits were recorded. Telephone consultations were permitted in patients unable to attend. Survival data were recorded from electronic records.

4.2.6 Sample Size and Statistical Considerations

As a feasibility trial, an *a priori* sample size calculation was not performed. The primary outcome measure (trial recruitment) was expressed as a mean monthly rate over the trial period and each 6-month interval. Secondary outcome measures were reported by descriptive statistics or proportions. 2x2 Contingency Tables were used to assess the sensitivity and specificity of *high* P_{EL} for NEL_{50} expressed as percentages with 95% confidence intervals. Statistical analyses were performed using GraphPad Prism v8.0.2 (San Diego, USA).

4.3 Results

4.3.1 Recruitment

Recruitment took place between August 2017 and September 2018. In total, 31 patients were recruited and randomised (16 to EDIT management (1 allocation failure – see Figure 4.3), 15 to Standard Care). The mean trial recruitment rate was 2.4 patients per month. The *a priori* primary objective of recruitment feasibility was achieved at week 35 at which point 15 patients had been recruited over the preceding 6 months (2.5 patients/month). A trial recruitment graph is shown in Figure 4.2 below.

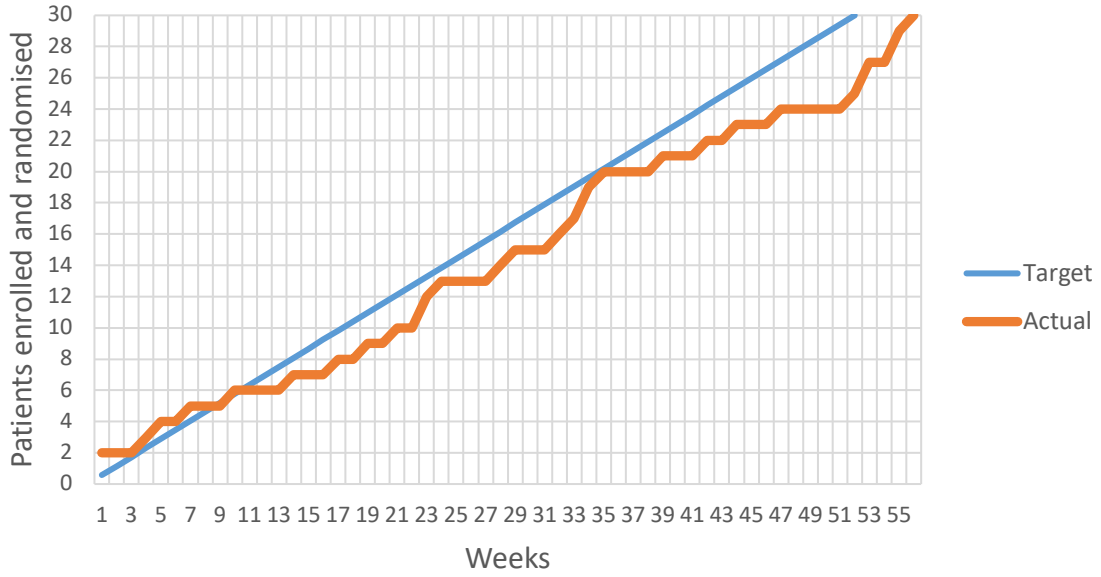


Figure 4.2 Recruitment to pre-EDIT from August 2017 to September 2018 plotted against target recruitment to achieve *a priori* feasibility threshold

4.3.2 Study Population

Baseline characteristics were similar between groups, particularly regarding age, tumour-type, performance status and symptoms (see Table 4.1). Patient flow is summarized by the CONSORT diagram below (Figure 4.3).

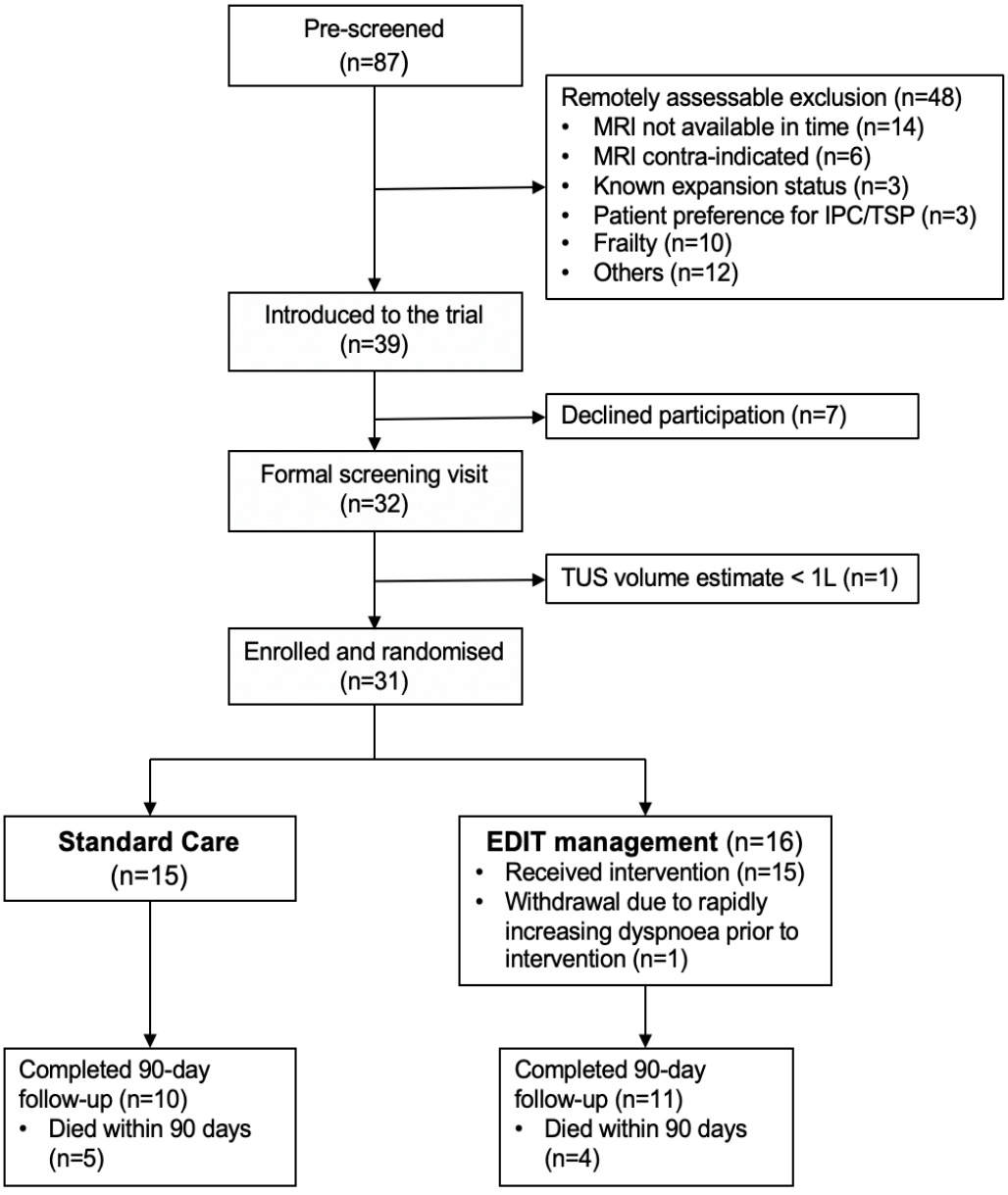


Figure 4.3 Pre-EDIT study flow chart

MRI, magnetic resonance imaging; IPC, indwelling pleural catheter; TSP, talc slurry pleurodesis; TUS, thoracic ultrasound scan; EDIT, elastance-directed indwelling pleural catheter or talc slurry pleurodesis; LVA, large volume aspiration.

Table 4.1 Pre-EDIT participant baseline characteristics

	Standard Care (n=15)	**EDIT (n=15)**
Age (median (range))	66 (48 – 90)	71 (51 – 90)
Male (n (%))	8 (53%)	4 (27%)
Right-sided (n (%))	12 (80%)	6 (40%)
Tumor type (n (%))		
Mesothelioma	1 (7%)	1 (7%)
Lung	6 (40%)	5 (33%)
Breast	3 (20%)	6 (40%)
Ovarian	1 (7%)	2 (13%)
Others	4 (27%)	1 (7%)
ECOG PS, number (n (%))		
0-1	11 (73%)	9 (60%)
2	2 (13%)	5 (33%)
3	2 (13%)	1 (7%)
VAS Dyspnoea (mm (SD))	50 (31)	47 (30)
VAS Pain (mm (SD))	17 (15)	19 (29)

EDIT, Elastance Directed Intrapleural catheter or Talc pleurodesis; ECOG PS, Eastern Cooperative Group Performance Status; VAS, Visual Analogue Score; SD, Standard Deviation

4.3.3 Technical feasibility

4.3.3.1 Elastance assessment

The mean time taken to complete P_{EL} assessment was 33 minutes (range 17–51 minutes). IPP data were incomplete in the first 2/15 EDIT patients due to a software reset mid-procedure. On both occasions, the device reset immediately following an episode of coughing during the procedure. The hypothesis that sharp elevations in IPP were responsible for the reset was confirmed after discussion with Rocket Medical engineers who advised that the device had been programmed to reset in response to measured pressures >30cmH_2O. A software update was performed to remove this reset threshold. Following this, complete data were acquired in the subsequent 13 cases. The procedural failure rate was therefore 2/15 (13%), but 0/13 (0%) after the software update.

4.3.3.2 Requirement for Boutin-type Needle

A single case (1/15, 7%) had insufficient residual pleural fluid following P_{EL} assessment to allow a definitive intervention using a standard Seldinger technique. In this case, a Boutin-type blunt pleural access needle, *without* pleural biopsy gate, was used to induce a pneumothorax. The Seldinger guidewire was then introduced into the pleural space via the needle following the removal of the blunt access stylet.

4.3.3.3 Target aspiration volume

Early iterations of the trial protocol (v2.0 (dated 4/3/2017) to v2.3 (dated 4/8/2017)) utilised a target maximum pleural aspiration volume while pleural manometry was performed (unless symptoms or IPP $\leq$ -20cmH_2O reached first). The target volume was calculated by subtracting 500ml from the ultrasound-based pre-procedure effusion volume estimate (see Section 2.4.11.3). This method was used to set an upper limit to aspiration during the management of pre-EDIT subjects 1-4. During the management of subject 4 (allocated to EDIT management) pleural aspiration was terminated when the target maximum aspiration volume was reached, however it was noted that a substantial residual effusion volume (subjectively far greater than 500ml) remained. Since the Goecke ultrasound volume estimate was derived from a series of drained effusions up to only 1650ml, it was judged that this technique was likely to have substantially underestimated the total effusion volume, thus leading to an

unnecessarily early termination of the DPM procedure and potentially compromising the sensitivity of the procedure to detect NEL, particularly in biphasic cases. A substantial amendment (resulting in protocol v2.4, dated 09/10/2017) was therefore implemented to replace the target maximum pleural aspiration volume with mid-procedure target ultrasound appearances in order to maximise the available manometry data for rolling P_{EL} calculation. This approach was adopted in all subsequent cases, although I continued to acquire US estimates of pre-drainage effusion volume for all subsequent cases. A detailed description of the aspiration volumes taken in pre-EDIT, the volumes required to detect abnormal P_{EL}, and a detailed assessment of the accuracy of the Goecke effusion volume estimate in pre-EDIT cases relative to volumetric MRI, are provided in Chapter 5.

4.3.4 Diagnostic performance of P_{EL250} for radiographic NEL

Pleural manometry data for patients who underwent EDIT management is summarised in Figure 4.4 below. *Normal* P_{EL} (<14.5cmH_2O/L at all stages) was recorded in 6/13 patients with complete data, of whom 0/6 subsequently developed NEL. *High* P_{EL} (≥14.5cmH_2O/L at any point) was recorded in 7/13 patients, of whom 4/7 developed NEL. Therefore, the pre-specified definition of *high* P_{EL} was associated with 100% sensitivity (95%CI 51-100%) and 67% specificity (95%CI 35-88%) for a subsequent a degree of NEL that would normally preclude an attempt at slurry pleurodesis (<50% pleural re-apposition). Figure 4.5 shows examples of (a) normal and (b) abnormal P_{EL} curves with corresponding radiographic appearances from EDIT management cases. In example (a), intra-pleural pressure (IPP) was recorded during aspiration of 2400ml, terminated at target ultrasound appearances (≤30mm visceral to costal distance). In this case, MaxP_{EL250} was 12cmH_2O/L (normal) therefore the patient was allocated to TSP and an ICD was inserted on the same day. The lung was fully re-expanded before discharge. In example (b), IPP was recorded during aspiration of 1400ml, terminated at the onset of excessive coughing. In this case, MaxP_{EL250} was 32cmH_2O/L (high) therefore the patient was allocated to IPC insertion on the same day. The lung failed to fully re-expand, as shown on follow-up radiograph at 14 days.

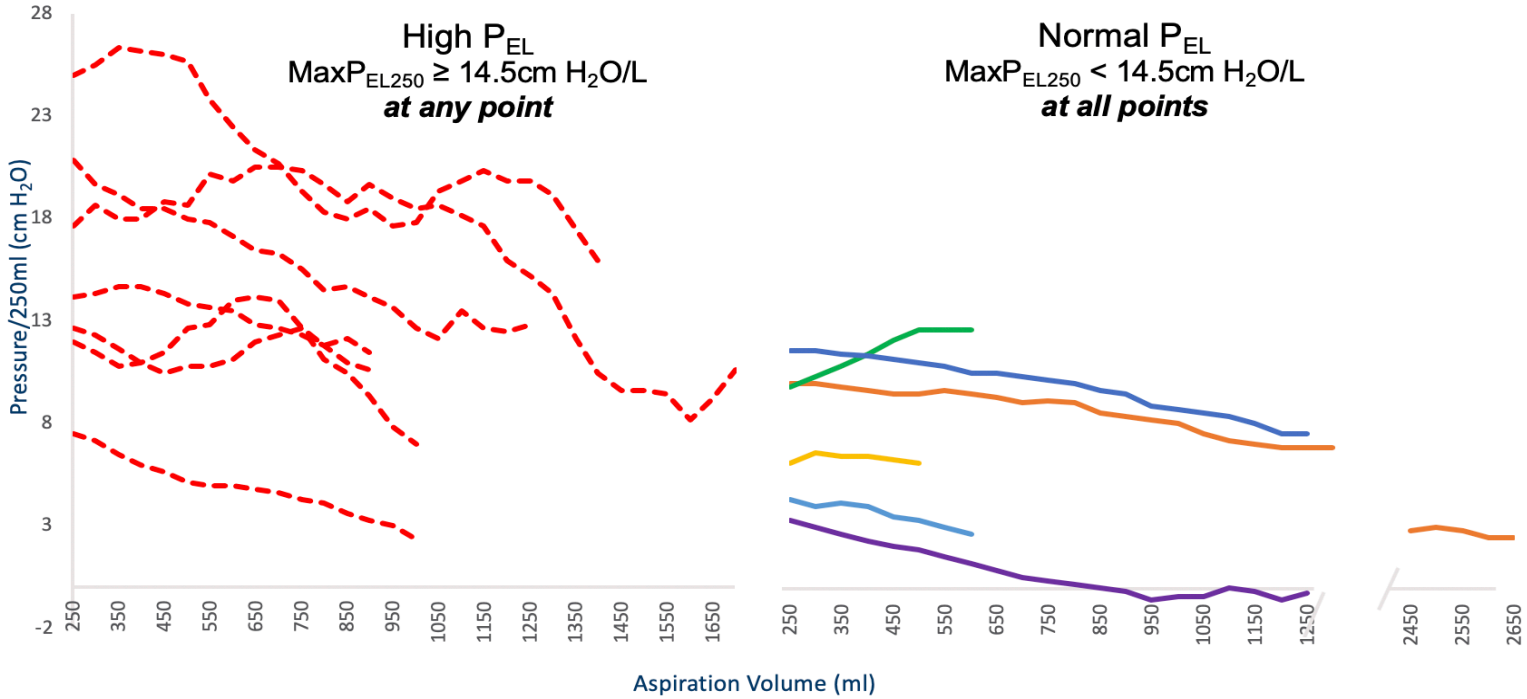


Figure 4.4 P_{EL} curves (IPP change / cavity volume change) were plotted in 13/15 EDIT cases with complete IPP data. P_{EL} was high ($MaxP_{EL250}$ ≥14.5cmH_2O/L at any point) in 7/13 patients, prompting same day IPC placement. P_{EL} was normal ($MaxP_{EL250}$ <14.5cmH_2O/L at all points) in 6/13 patients, prompting same day ICD insertion for subsequent TSP. High P_{EL} curves are shown on the left x-axis and normal P_{EL} curves on the right x-axis.

P_{EL}, pleural elastance; EDIT, elastance-directed indwelling pleural catheter or talc slurry pleurodesis; IPP, intrapleural pressure; $MaxP_{EL250}$, maximum pleural elastance sustained over a 250ml aspiration volume at any point during a large volume aspiration; IPC, indwelling pleural catheter; ICD, intercostal chest drain; TSP, talc slurry pleurodesis.

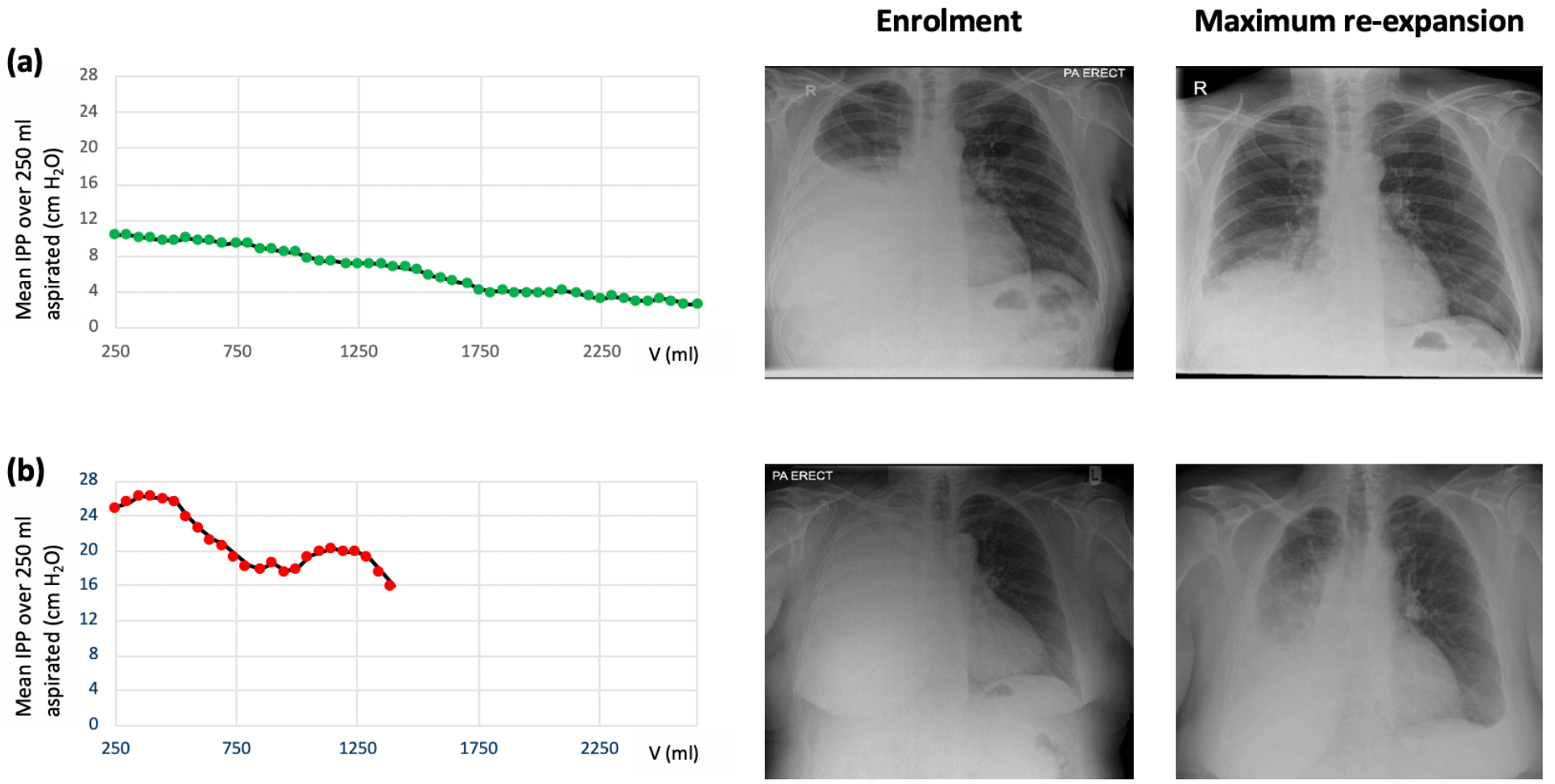


Figure 4.5 Examples of (a) normal and (b) abnormal P_{EL} curves with corresponding radiographic appearances from EDIT management cases

4.3.5 Safety

Pleural aspiration was terminated at target volume or ultrasound appearances in 11/15 (73%) and due to persistent cough in 4/15 (27%). Chest pain led to termination in 0/15 cases. No serious adverse events (SAEs) directly attributable to EDIT were reported. A summary of all adverse events is presented in Table 4.2. 1/15 (7%) cases had insufficient fluid for immediate IPC placement using a standard Seldinger technique. In this case, a 'Boutin-type' needle was used for pneumothorax induction prior to IPC placement without any complication. As previously discussed, a standard Boutin needle was unsuitable for this purpose as the integrated pleural biopsy gate may have caused trauma to the chest wall if removed over the guidewire since the gate would not be sufficiently occluded by the wire.

Table 4.2 Summary of all adverse events within the pre-EDIT trial

Date	Study ID	Classification	Severity	Related to trial interventions	Description of event and outcome
18/9/17	3	AE	Mild	Definitely	Sensor reset due to high IPP during coughing. Procedure completed without further incident but IPP data discontinuous and therefore unsuitable for further analysis.
27/9/17	4	AE	Mild	Definitely	Sensor reset due to high IPP during coughing. Procedure completed without further incident but IPP data discontinuous and therefore unsuitable for further analysis.
28/11/17	7	AE	Mild	Definitely	Leakage of a few drops of pleural fluid from 3-way tap during manometry procedure. 3-way tap replaced, and procedure completed without further incident.
1/12/17	3	SAE	Moderate	Unrelated	Patient admitted with community acquired pneumonia.
7/3/18	15	AE	Mild	Probably	Minor asymptomatic subcutaneous swelling at site of manometry catheter insertion. Resolved within 8 days.
6/4/18	17	AE	Mild	Definitely	Sensor reset following cough after removal of 100ml fluid. Manometry catheter was removed, recalibrated and re-inserted without compromising asepsis. Manometry data incomplete and therefore unsuitable for further analysis. No clinically adverse consequences.
11/4/18	18	AE	Mild	Definitely	Leakage of a few drops of pleural fluid from manometry catheter one-way valve following removal of verres introducer needle. No clinically adverse consequences.

11/4/18	18	AE	Mild	Definitely	Difficulty inserting manometry catheter. Required use of Seldinger dilation kit, prolonging the procedure by approximately 1 minute. No clinically adverse consequences.
20/4/18	11	SAE	Moderate	Possibly related	Patient with lung cancer admitted with abdominal pain and swelling. CT scanning revealed widespread disease progression despite recently initiated anti-PDL1 immunotherapy. This included multiple sites of visceral disease, plus disease in the chest wall and flank ipsilateral to the trial intervention. It was considered possible that these findings may have reflected procedure tract metastases, but the pattern was that of widespread disease progression, possibly anti-PDL1 hyper-progression.
2/9/18	27	SAE	Moderate	Unrelated	Patient re-admitted with a combination of nausea, vomiting and unsteadiness. Presenting symptoms likely due to dihydrocodeine use and constipation.

AE, adverse event; SAE, serious adverse event; IPP, intrapleural pressure

4.4 Discussion

4.4.1 Feasibility of investigating the efficacy an elastance-directed treatment pathway for MPE

4.4.1.1 Recruitment

Pre-EDIT was a positive study which has demonstrated the feasibility of recruitment to an RCT in which patients with symptomatic MPE are randomised between an elastance-directed treatment pathway (EDIT) and inpatient TSP. The *a priori* primary objective was achieved through trial enrolment, randomisation and delivery of per protocol definitive pleural intervention to 15 patients within a 6 month period (2.5/month). The overall trial recruitment of 31 patients over 12 months (with only 1 allocation failure) equates to a mean recruitment rate of 2.4 participants/month. This is considerably higher than the median recruitment rate reported in UK randomized controlled trials (0.92 participants/month (IQR 0.43-2.79)) [96] and compares favourably to recently reported multicentre MPE trials (0.26 and 0.60 participants/month/centre, for IPC-PLUS [93] and AMPLE [3], respectively), suggesting that the EDIT design is feasible to deliver in reasonable numbers.

4.4.1.2 Sample size for phase III study

Pre-EDIT was designed to test whether a recruitment rate of 2.5 participants/month could be achieved at a single centre. Although this exact figure was somewhat arbitrary, it was chosen since if up scaled to a practically deliverable multicentre trial, this RCT design would be likely to deliver a sufficiently large sample to robustly assess the efficacy of EDIT management.

A definitive study of EDIT efficacy would require the use of a clinically relevant patient-centred primary outcome measure, such as need for repeat pleural intervention for symptomatic recurrence within 3 months. For example, in order to detect a reduction in TSP failure rate from 25% in the control arm (TSP, based on rates in previous studies of 22-29% [3,5]) to 10% in the intervention arm (EDIT), with 90% power, a 2-sided α=0.05, and assuming a 10% loss to follow-up (3% in TAPPS [26], 17% in TIME-1 [27]), 292 patients will be required (146 in each arm). Given the findings from pre-EDIT, such a trial would be deliverable within the well-developed pleural research networks in the UK, Europe and the US over

10-12 sites recruiting for 24 months. Furthermore, since MRI contraindications accounted for 20/48 (42%) pre-screen failures in pre-EDIT, and MRI would not be performed in a Phase III trial, the recruitment rate may be considerably higher.

4.4.1.3 Technical deliverability and safety

In total, fifteen patients underwent EDIT management within pre-EDIT. P_{EL} assessment, calculation of P_{EL250} and delivery of an elastance-directed definitive pleural intervention was successfully completed in 13/15 patients (87%), and in all patients (13/13) following an early software update to the digital pleural manometry equipment. In all EDIT cases with complete data (13/15), elastance-directed management (IPC or ICD) was delivered on the same day as P_{EL} assessment and there were no procedure-related SAEs. Boutin-type needle pneumothorax induction was required prior to definitive management in only one case. These findings support the assertion that EDIT management is potentially widely deliverable should its efficacy be demonstrated. Additionally, in pre-EDIT, the (MRI-incompatible) manometry catheter had to be removed before placement of the elastance-directed treatment (IPC or ICD). In future delivery of EDIT management, a guidewire could simply be placed through the lumen of the manometry catheter facilitating immediate exchange for an IPC or ICD, greatly improving the efficiency and risk profile of the pathway. Further potential refinements to the EDIT pathway are discussed in Chapter 5.

4.4.2 Relationship to Previous Studies

Pre-EDIT is the first comparative study that has allocated patients to TSP or an IPC based on any biomechanical marker of lung expansion potential. Although Lentz *et al* recently reported an important negative randomised Phase III trial testing the effect of manometry-directed thoracentesis on chest pain, [76] no attempt was made in their study to direct definitive management based on IPP data.

4.4.2.1 Diagnostic performance of P_{EL250} for radiographic NEL

Pre-EDIT was not designed to detect radiographic NEL. As detailed in Chapter 3, radiographic NEL is associated with poor inter-observer agreement and has not been correlated with patient-centred outcomes; it is therefore inherently unsuitable as a trial outcome measure. However, a *post hoc* analysis of the diagnostic performance of P_{EL} for NEL was used to indirectly assess the

suitability of the novel abnormal elastance definition (P_{EL250} ≥ upper limit of normal P_{EL} (14.5 cm H_2O/L)) prior to utilising this in a future trial. Accepting the limitation of radiographic NEL as a poor surrogate for pleurodesis failure, it is logical to compare the NEL diagnostic performance data obtained in pre-EDIT to that from previous studies.

In an earlier prospective observational study using an improvised manometer, Lan *et al* reported that elevated P_{EL} (a single point estimate ≥19 cm H_2O/L) during removal of 500ml fluid was associated with 79% sensitivity and 94% specificity for NEL. [67] Using the same P_{EL} threshold but averaged over complete effusion drainage, Salamonsen *et al* reported lower sensitivity (40%) but 100% specificity for NEL. [94] The P_{EL} threshold used to allocate cases to IPC in pre-EDIT was intentionally lower (≥ 14.5 cm H_2O/L) than in both of these studies in order to increase sensitivity to a degree of NEL that would normally preclude slurry pleurodesis. This reflected the view that false positive high P_{EL} was a 'lesser evil', simply resulting in IPC placement in those with expansile lung, which may be amenable to subsequent ambulatory pleurodesis. False negative results, conversely, would lead to a futile hospital admission for attempted TSP. Furthermore, in contrast to Lan *et al*, the use of a large aspiration volume in pre-EDIT was designed to identify delayed abnormal physiology, or 'biphasic NEL', [50] which might only be evident on removal of larger volumes. The finding of high sensitivity (100% (95% CI 51-100%)) is encouraging in this regard, but requires cautious interpretation given the underpowered and *post hoc* nature of this analysis. This sensitivity is also far higher than that reported by Chopra *et al* using the same P_{EL} threshold (≥ 14.5 cm H_2O/L) for NEL diagnosis (sensitivity 71% (95% CI 55-83%)), however in their study a more stringent definition of expansile lung (≥ 90% expansion) was adopted, which is likely to be the principle reason for the discrepancy in sensitivity seen here. [60] Additionally, a rolling average P_{EL} was adopted in pre-EDIT in an attempt to mitigate against a predictable reduction in specificity, by requiring a sustained increase in elastance (over at least 250ml) to diagnose NEL. Although the reported specificity (67% (95% CI 35-88%)) is lower than in previous studies, the novel P_{EL250} definition arguably represents a logical compromise worthy of further large-scale investigation given the previously described clinical imperative to prioritise sensitivity.

4.4.3 Study Strengths and Limitations

Pre-EDIT was a prospective RCT conducted in accordance with CONSORT guidelines and reported transparently throughout, including clinical trial registration (clinicaltrials.gov) and publication of the trial protocol. As a feasibility trial, pre-EDIT recruited a small sample resulting in inevitably wide confidence intervals relating to radiographic NEL prediction and clearly this also precluded an assessment of alternative P_{EL} thresholds or definitions. Nonetheless, pre-EDIT was able to robustly assess its primary objective of recruitment feasibility and refine technical aspects of the novel EDIT pathway design which are discussed further in Chapter 5.

4.4.4 Conclusions

Pre-EDIT is the first prospective randomised controlled trial to examine P_{EL}-directed MPE management. This work has demonstrated the feasibility of a definitive phase III trial, representing a significant first step towards a personalised treatment pathway for patients with MPE. The delivery of a definitive study of EDIT management efficacy is feasible in terms of both expected recruitment and technical deliverability. From this finding, it follows that experience from the delivery of pre-EDIT, and data relating to secondary and exploratory objectives, should be used to further optimise the EDIT pathway prior to a definitive study. These suggested developments and supporting data are discussed in Chapter 5.

Chapter 5

OPTIMISATION OF AN ELASTANCE-DIRECTED MANAGEMENT PATHWAY FOR MALIGNANT PLEURAL EFFUSION

5 Chapter 5: Optimisation of an elastance-directed management pathway for malignant pleural effusion

5.1 Introduction

Pre-EDIT has been the first prospectively conducted trial in which definitive malignant pleural effusion (MPE) management was delivered to patients on the basis of a pre-drainage prediction of lung re-expansion potential. The successful conduct of this trial, detailed in Chapter 4 of this thesis, demonstrates the suitability of key elements of this study design for use in future research. As a wholly novel concept, the development of the EDIT management pathway necessarily encompassed a number of areas of uncertainty. It is also noteworthy that pre-EDIT represented the first clinical use of the Rocket Medical digital pleural manometer (DPM) and the performance of this equipment *in vivo* was hitherto unknown. Pre-EDIT therefore provided an invaluable opportunity to thoroughly test the practicality of EDIT management, identify any unforeseen shortcomings, and test possible solutions in order to increase the reliability and efficiency of EDIT delivery.

As previously discussed in this thesis, several trials and a subsequent meta-analysis have shown equivalent symptom relief and survival between those patients with MPE managed with first-line talc slurry pleurodesis (TSP) and those managed with indwelling pleural catheter (IPC) drainage. [39] Since a significant minority of patients undergoing TSP experience treatment failure due to occult non-expansile lung (NEL), it follows that pre-drainage exclusion of NEL may enhance TSP success rates in patients without NEL, and direct those with NEL away from the possible harms of futile TSP and towards a more appropriate first-line IPC management strategy. EDIT management was developed to realise these theoretical advantages. In doing so, the following assumptions were made:

- Where possible, a significant proportion of patients would prefer TSP over IPC i.e. first-line IPC management is not universally acceptable
- Pleural elastance (P_{EL}) is the optimal biomarker for NEL detection
- The definition of P_{EL} (the change in intra-pleural pressure (IPP) for a given pleural aspiration volume during thoracentesis (V_{OUT})) correctly

assumes V_{OUT} is an accurate reflection of the true pleural cavity volume change which occurs during thoracentesis

- A near-maximal aspiration volume is required in order to achieve an acceptable degree of sensitivity and specificity for the detection of NEL using P_{EL}
    - This objective may be achieved using a target aspiration volume based on a pre-procedure estimate of MPE volume calculated from bedside TUS measurements

The rationale behind each assumption based on available literature is outlined in this introduction.

5.1.1 Patient preferences in the management of MPE

Given established evidence regarding the clinical equivalence (based on symptom scores and survival) of TSP and IPC insertion in management of symptomatic MPE, [39] international guidelines universally highlight the importance of individualised shared decision-making for this patient group. [46,47] However, there is no published data to indicate what proportion of patients might choose inpatient TSP when provided with objective information and an unbiased offer of either option. Early patient survey data from the Oxford pleural unit, where both inpatient TSP and IPC insertion are routinely offered to patients with symptomatic MPE, indicates that the majority of patients (18/26 in their series) opted for TSP. [43] Of those patients who chose TSP, over half indicated they would not consider IPC insertion, and 80% of those surveyed felt outpatient management would either have no effect, or a negative effect, on their quality of life. [43] While broadly supportive of further work to enhance inpatient TSP success rates, these data must be interpreted with caution given the small number of cases involved. Collection of further data on patient preferences for MPE management is therefore important to guide future research to improve relevant patient outcomes. The results of a Treatment Preferences Survey embedded within the pre-EDIT trial contributes to this knowledge-base and is presented in this Chapter.

5.1.2 Pleural elastance performance relative to Ultrasound measures

The choice of P_{EL} assessment, rather than non-invasive imaging techniques, to detect NEL is discussed and justified in Chapter 4, Section 4.1. However, the opportunity was taken during the conduct of pre-EDIT to acquire comparative M-mode TUS images. These data are reported in this chapter.

5.1.3 Validation of P_{EL} definition

P_{EL} is currently defined indirectly, based on the assumption that the change in pleural cavity volume during thoracentesis is exactly equal to the volume of pleural fluid that is removed. This definition assumes that unmeasured liquid (e.g. pleural fluid, blood, local anaesthetic) or gases (e.g. air from the environment or lung parenchyma) are neither added nor lost from the pleural cavity during the conduct of pleural manometry. Clinical experience would suggest that these assumptions are probably valid in the majority of cases, perhaps except in those where there is significant lung entrapment and transient air ingress across the visceral surface. Nonetheless, pre-EDIT provided a unique opportunity to validate these assumptions directly further using volumetric MRI pre- and post-thoracentesis. In this chapter the true pleural cavity volume change derived using these measurements (ΔV_{MRI}) is compared with aspiration volumes (ΔV_{OUT}) in patients undergoing EDIT management. Analysis of these data are essential in understanding the diagnostic performance of P_{EL} and further optimising the DPM technology used.

5.1.4 Selection of the optimal aspiration volume for EDIT management

Selection of the optimal aspiration volume for EDIT management introduces an inherent compromise between maximising the diagnostic performance of P_{EL} data (sensitivity will increase as aspiration volume rises) and the technical ease, and importantly, the safety of the subsequent definitive pleural intervention. This is because Seldinger insertion techniques involve more risk of damage to intrathoracic organs when the volume of the effusion being drained is small.

Since pre-EDIT adopted a novel definition of abnormal P_{EL} ($MaxP_{EL250} \geq 14.5$ cmH_2O/L, see discussion in Chapter 4, section 4.4.2.1), the minimum aspiration volume required to reliably detect abnormal P_{EL}, where present, was unknown prior to the study. The protocol therefore directed as large an aspiration volume

as possible while retaining the technical feasibility of Seldinger drain insertion (ICD or IPC). This was because a frequent requirement for pneumothorax induction, using a Boutin-type needle to facilitate safe blunt pleural access, would seriously compromise deliverability of routine EDIT management. This aim was achieved through the use of a target aspiration volume; initially based on an ultrasound based estimate of pleural effusion volume (detailed in Chapter 1, section 2.10) [87] and latterly, following experience during the trial conduct, based on serial mid-procedure thoracic ultrasound (TUS) measurements. This Chapter reports both the range of aspiration volumes required to detect abnormal P_{EL} (where present), and the accuracy of the Goecke TUS pleural effusion volume estimate initially used, but subsequently abandoned for clinical decision making. The implications of this data on future trial design are discussed.

5.2 Materials and methods

The data in this chapter were acquired during the pre-EDIT study which is described in detail in Chapter 2. Specifically, the methods pertaining to these results are detailed in:

- Sections 2.4.5.1, 2.4.5.4 and 2.4.6.2 regarding the Treatment Preferences Survey
- Sections 2.4.11.1 M-mode ultrasound, section 2.4.11.3 DPM, and section 2.4.16 regarding radiographic NEL definition
- Section 2.4.11.2 and section 2.4.11.4 Volumetric MRI acquisition and analysis
- Section 2.4.11.1 Goecke TUS effusion volume estimate (see also Appendix 7)

5.2.1 Patient preferences

As described in section 2.4.5.1, consecutive patients with symptomatic MPE who were pre-screened for participation in pre-EDIT were invited to complete a short semi-structured survey of their preferences with regards to MPE treatment. The TPS is shown in appendix 5.

5.2.2 Performance of TUS in the detection of NEL

M-mode TUS assessment was undertaken in pre-EDIT participants allocated to EDIT management prior to thoracentesis and DPM. The method of TUS image acquisition and analysis is detailed in section 2.4.11.1. Following TUS and MRI scanning, thoracentesis (see TSI in appendix 7) was performed with pleural manometry measurements taken at 50ml intervals as described in section 2.4.11.3.

Following definitive intervention (IPC insertion or ICD followed by complete pleural drainage and attempted TSP), NEL was defined by the appearance of the post-ICD removal, pre-discharge CXR in those receiving TSP, or the CXR obtained 14 days from discharge in those who underwent IPC insertion. Radiographs were classified by me using subjective visual estimation as showing:

- Expansile lung (>75% expansion)
- NEL_{75} (<75% but >50% expansion)
- NEL_{50} (<50% expansion)

As described in section 2.4.24.2, 2x2 contingency tables were used to calculate the sensitivity and specificity of *high* P_{EL} for NEL_{50} whereas the diagnostic performance of M-mode lung excursion for NEL_{50} and NEL_{75} was expressed as area under the ROC curve.

5.2.3 Validation of P_{EL} definition

This work was performed in patients allocated to EDIT management which is described fully in section 2.4.11.

5.2.3.1 MRI acquisition

Pre- and post-DPM volumetric MRI scanning was performed according to the imaging protocol detailed in sections 2.4.11.2 and 2.4.11.4.

5.2.3.2 MRI Phantom

To provide a reference standard for MRI volumetric data acquired in pre-EDIT, a deformable trial-specific pleural cavity MRI phantom was developed by collaborators from the NHS MR Physics Group, NHS Greater Glasgow and Clyde. The MRI phantom is discussed in more detail in section 2.4.14.

5.2.3.3 MRI analysis

The pleural cavity volume change (ΔV_{MRI}) was defined as the difference between the pre- and post-aspiration pleural cavity volumes on T1 VIBE images. The volumetric analysis was performed using Myrian® software v2.0 (Intrasense®, Montpellier, France) as described in section 2.4.13. Briefly, in each EDIT case, the volume of the pleural cavity pre- and post-DPM was measured. A free-hand tool was used to outline a region of interest 'contour mask' over the pleural cavity on approximately every fourth or fifth axial image. The region of interest contour mask was then extended through the complete image series semi-automatically to create a 3-dimensional contour mask; the volume of which was automatically calculated by the Myrian® software. The accuracy of this contour

mask was visually assessed, and small adjustments made using free-hand drawing tools, if required, prior to the cavity volume being recorded.

5.2.3.4 MRI volumetric analysis reproducibility

The MRI volumetric analysis described above was repeated by a second independent operator (WH, ST5 radiologist) who was blinded to the results of my analysis. The Bland-Altman method was used to assess agreement between operators to establish the reproducibility of this technique.

5.2.3.5 Comparison between V_{OUT} and ΔV_{MRI}

V_{OUT} was calculated from the mass of aspirated fluid based on individual estimates of fluid density derived from each effusion's protein concentration as described in section 2.4.12. Agreement between V_{OUT} and ΔV_{MRI} were made using the Bland-Altman method.

5.2.4 Selection of Optimal Aspiration Volume

Again, this work was based on data acquired from pre-EDIT participants randomised to EDIT management. In each case, prior to DPM, an estimate of total effusion volume was made using the Goecke formula (V_{TUS}) based on TUS measurements of the lateral and sub-pulmonic effusion dimensions as per the TSI shown in Appendix 7. [87] Agreement between V_{OUT} and pre-DPM V_{MRI} were made using the Bland-Altman method.

Additionally, the aspiration volume was recorded at which abnormal P_{EL250} (i.e. >14.5 cm H_2O/L), where present, was first reached.

5.3 Results

5.3.1 Patient preferences

TPS participation commenced on 7th March 2018 (approximately 7 months after pre-EDIT had opened to recruitment) and concluded with the recruitment of the final patient to pre-EDIT on 18th September 2018. A total of 17/40 potentially eligible patients (43%) completed the pre-EDIT TPS. 13/17 (76%) participated in the full pre-EDIT trial and 4/17 (24%) completed the TPS following an invitation to do so at pre-screening.

All TPS respondents (17/17 (100%)) indicated that they had been provided with sufficient information to make a decision about their treatment. All respondents (17/17 (100%)) also indicated that their preference would be to receive an inpatient talc slurry pleurodesis. The majority (9/17 (53%)) cited the avoidance of 'long term' indwelling prosthetic material (if TSP were successful) as their principle reason for choosing first line TSP. Lower risk of infection (5/17 (29%)), less discomfort in the long term (1/17 (6%)) and a requirement for care of the drain site and a 'reminder' of their illness (1/17 (6%)) were also reported as reasons to favour TSP. The rationale for their treatment preference was left unanswered by a single respondent.

The next section of the questionnaire outlined the findings of the IPC-PLUS trial [48] and asked respondents to indicate whether they would change their initial decision for first-line inpatient TSP if an attempt at outpatient TSP via an IPC (following the IPC-PLUS protocol) were offered to them. 4/17 (24%) indicated they would change their mind and choose an IPC-based strategy while the remaining 13/17 (76%) said their preference would remain an attempt at inpatient TSP. When asked whether they would consider a 2-stage pleural intervention process incorporating pleural manometry and an assessment of P_{EL}, the vast majority (15/17 (88%)) indicated they would consider this an acceptable treatment, with 2 participants stating they were already content with their decision would not want to have a second procedure.

5.3.2 Performance of TUS in the detection of NEL

M-mode sonographic assessment of pre-aspiration atelectatic lung excursion due to transmitted cardiac impulse was successfully recorded in 10/15 (67%) patients

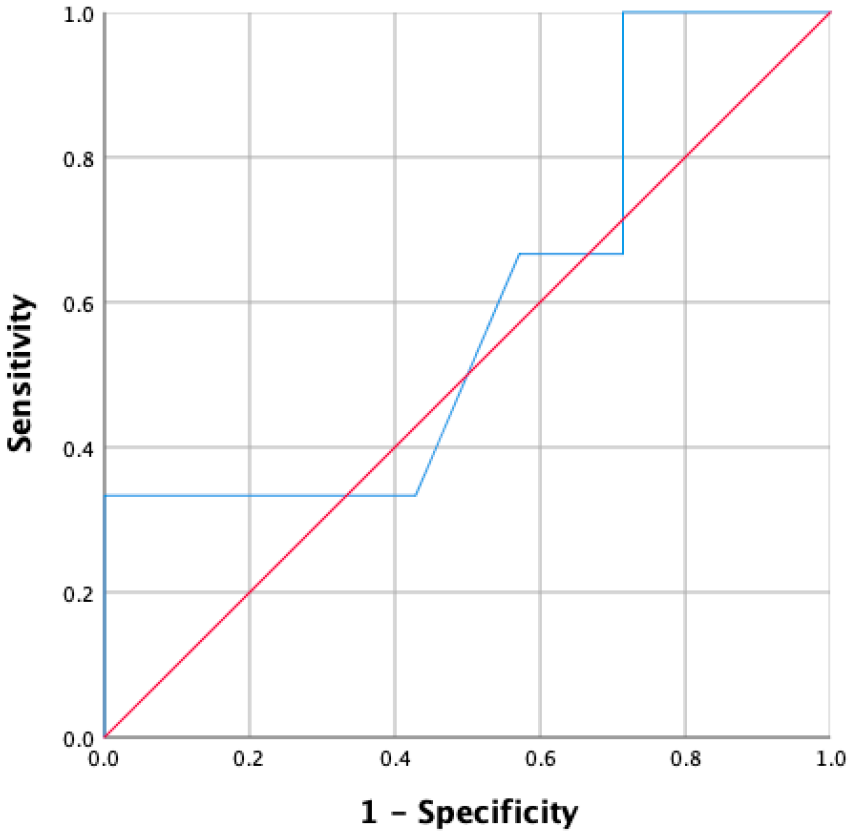
who received EDIT management. Missing data was attributed to failure to save images (2/15 (13%)), an inadequate sonographic window (2/15 (13%)), and an inability to analyse M-mode recording due to breathing artefact (1/15 (7%)). The range of lung excursion encountered and associated subsequent radiographic lung re-expansion classification is shown in Table 5.1. The area under the ROC curves (Figure 5.1) for M-mode lung excursion prediction of subsequent NEL_{50} was 0.595 (95% CI 0.180-1.000) and 0.680 (95% CI 0.328-1.000) if NEL was defined as NEL_{75}.

Table 5.1 Measured atelectatic lung excursion due to cardiac impulse measured by M-mode ultrasonography in EDIT management cases (n=10) and associated final post-drainage radiographic lung re-expansion classification

Subject number	**Atelectatic lung excursion (mm)**	**NEL_{50}**	**NEL_{75}**
3	2.30	Absent	Present
4	3.50	Present	Present
7	3.70	Absent	Absent
10	2.30	Present	Present
11	2.50	Absent	Absent
15	2.20	Absent	Absent
19	4.20	Absent	Absent
27	1.43	Absent	Present
28	1.23	Absent	Absent
29	0.51	Present	Present

M-mode, Motion-mode; EDIT, Elastance Directed Intrapleural catheter or Talc pleurodesis; NEL_{50}, non-expansile lung defined by $\leq$ 50% pleural apposition; NEL_{75}, non-expansile lung defined by $\leq$ 75% pleural apposition

(a)



(b)

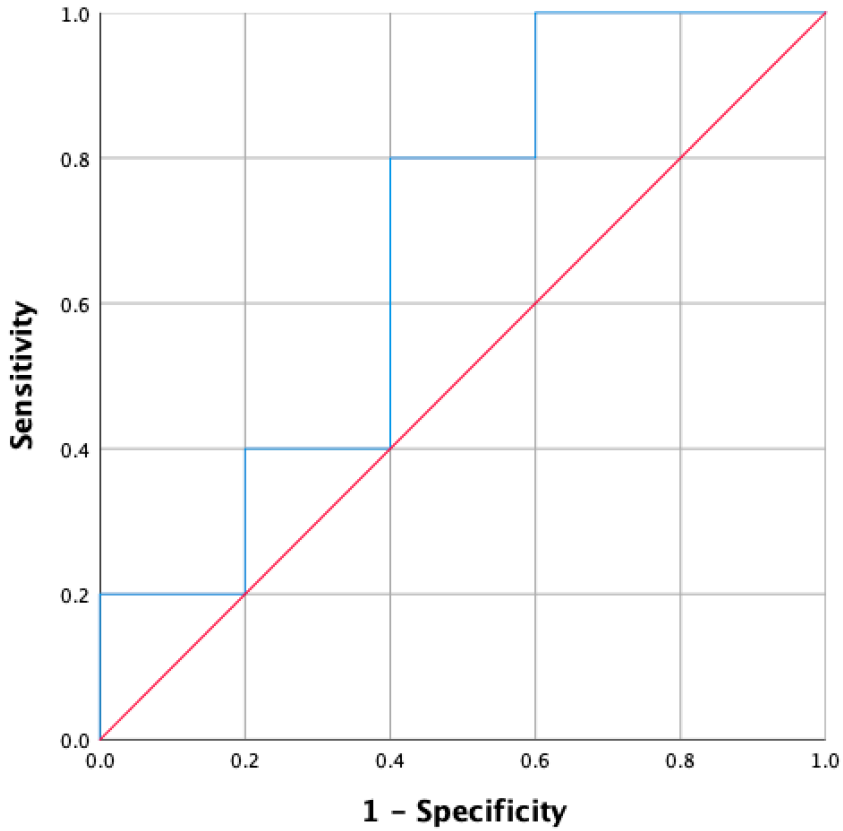


Figure 5.1 ROC curves for atelectatic lung excursion, due to cardiac impulse measured by M-mode ultrasonography, prediction of subsequent (a) NEL_{50} and (b) NEL_{75} in EDIT management cases (n=10)

5.3.3 Validation of P_{EL} definition

5.3.3.1 MRI acquisition

A standard MRI protocol was used for all patients, as summarised in Methods sections 2.4.11.2 and 2.4.11.4. At deployment, Field-of-View (FoV), slice thickness and the number of slices were adjusted to accommodate the size of each patient's thorax. FoV varied from 400mm to 459mm. Slickness varied from 1.8mm to 2.0mm. The number of slices varied from 104 to 128. Complete volumetric T1 VIBE MRI sequences were acquired in 12/15 (80%) EDIT subjects; 1/15 (7%) missed their allocated MRI scanning appointment due to a delayed inter-hospital transfer, 1/15 (7%) was unable to tolerate MRI scanning due to orthopnoea, and 1/15 (7%) had incomplete image acquisition (lower border of costophrenic recess erroneously omitted from scanned volume). ICC between assessor measured volumes are shown in Table 5.3.

5.3.3.2 MRI Phantom

As previously described, this work was performed entirely by collaborators in the MR Physics Group without my direct involvement. The percentage error associated with measuring the dynamic phantom fluid volume on T1 VIBE imaging using Myrian® software ranged from 0.6% to 16.7%. Smaller fluid volumes were associated with a larger percentage error. Where fluid volumes of 500 – 1000ml were analysed, the percentage error ranged from 0.6% to 6.4%.

5.3.3.3 MRI analysis

The pleural cavity volumes measured pre- and post-aspiration are presented in Table 5.2.

Table 5.2 Pleural cavity volumes measured on volumetric T1 VIBE MRI pre- and post-aspiration by primary (GAM) and secondary (WH) assessors in EDIT management subjects with complete imaging (n=12)

Subject number	Pre-aspiration volume GAM (ml)	Post-aspiration volume GAM (ml)	ΔV_{MRI} GAM (ml)	Pre-aspiration volume WH (ml)	Post-aspiration volume WH (ml)	ΔV_{MRI} WH (ml)
3	1861	686	1175	2156	1148	1008
4	4313	2904	1409	4489	2950	1539
7	1910	1049	861	2143	1001	1142
8	1569	642	927	1729	717	1012
10	1813	965	848	1786	796	990
11	4533	2263	2270	4671	2246	2425
15	2082	891	1191	2114	877	1237
19	1157	667	490	1312	690	622
26	1784	967	817	1955	1037	918
27	979	484	495	1006	493	513
28	1020	435	585	1164	502	662
32	1706	516	1190	1711	543	1168

ΔV_{MRI}, change in pleural cavity volume measured by pre- and post-aspiration volumetric magnetic resonance imaging

5.3.3.4 MRI reproducibility

Agreement between primary and secondary assessors is summarised as intra-class correlation coefficients in Table 5.3.

Table 5.3 Inter-observer agreement of semi-automated volumetric assessment of pleural cavity volumes performed by primary (GAM) and secondary (WH) assessors

	ICC	**95% CI**
GAM vs WH pre-aspiration	0.997	0.988-0.999
GAM vs WH post-aspiration	0.981	0.936-0.994
GAM vs WH ΔV_{MRI}	0.976	0.918-0.993

ICC, Intraclass Correlation Coefficient; 95% CI, 95% Confidence Interval

5.3.3.5 Comparison between V_{OUT} and ΔV_{MRI}

The change in pleural cavity volume inferred from the volume of fluid aspirated (V_{OUT}) and corresponding change in pleural cavity volume measured on volumetric MRI (ΔV_{MRI}) by the primary assessor (GAM) are recorded in Table 5.4. The agreement between V_{OUT} and ΔV_{MRI} are presented as a Bland-Altman plot in Figure 5.4.

Table 5.4 Change in pleural cavity volume inferred from fluid aspiration volume (V_{OUT}) and measured by volumetric MRI (ΔV_{MRI}) in EDIT cases with complete MRI acquisition (n=12)

Subject number	**ΔV_{MRI} (ml)**	**V_{OUT} (ml)**	**ΔV_{MRI} - V_{OUT} (ml)**
3	1175	1236	-61
4	1409	1292	117
7	861	820	40
8	927	846	81
10	848	876	-28
11	2270	2427	-157
15	1191	1102	89
19	490	482	8
26	817	816	1
27	495	480	15
28	585	565	20
32	1190	1127	63

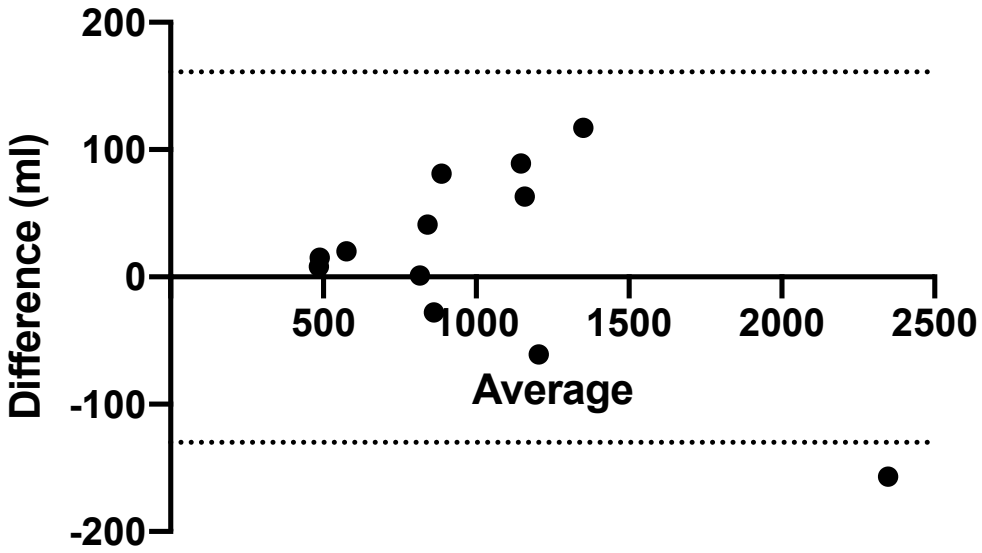


Figure 5.2 Bland-Altman plot showing agreement between change in pleural effusion volume inferred from fluid aspiration volume (ΔV_{OUT}) and measured by volumetric MRI (ΔV_{MRI}) in EDIT cases with complete MRI acquisition (n=12)

Dotted lines indicate 95% Limits of Agreement

5.3.4 Selection of Optimal Aspiration Volume

5.3.4.1 Agreement between V_{TUS} and V_{MRI}

Pre-aspiration TUS estimates of effusion volume (V_{TUS}), and corresponding pleural cavity volume measured on MRI (V_{MRI}) by the primary assessor, are recorded in Table 5.5. Agreement between V_{TUS} and V_{MRI} are presented as a Bland-Altman plot in Figure 5.3.

Table 5.5 Pre-aspiration pleural effusion volume estimated by Goecke thoracic ultrasound method (V_{TUS}) and measured by volumetric MRI (V_{MRI}) in EDIT cases with complete MRI acquisition (n=12)

Subject number	**V_{MRI} (ml)**	**V_{TUS} (ml)**	**V_{MRI}-V_{TUS} (ml)**
3	1861	2023	-162
4	4313	2002	2311
7	1910	1862	48
8	1569	1897	-328
10	1813	1652	161
11	4533	2478	2055
15	2082	2394	-312
19	1157	1309	-152
26	1784	1568	216
27	979	1820	-841
28	1020	1603	-583
32	1706	1638	68

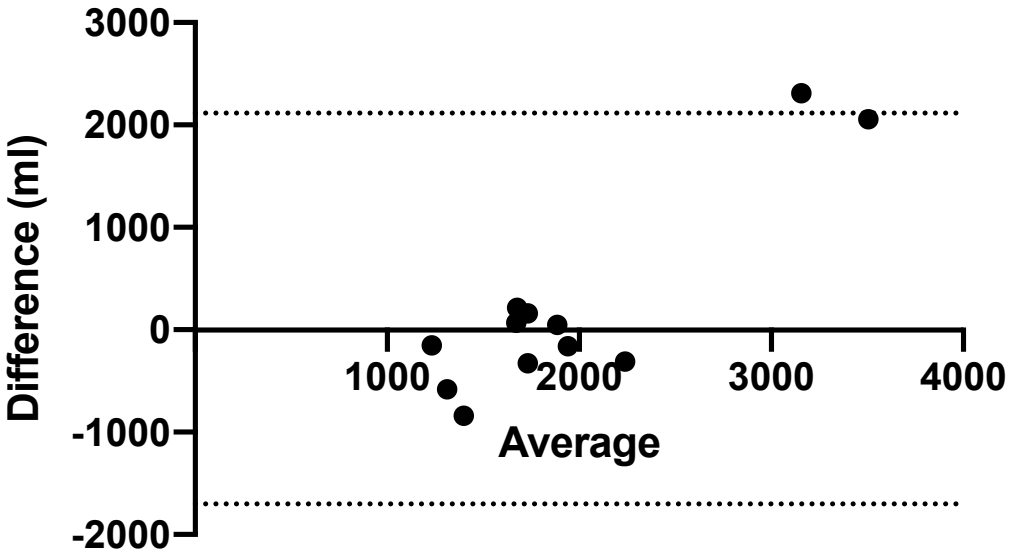


Figure 5.3 Bland-Altman plot showing agreement between pre-aspiration pleural effusion volume estimated by Goecke TUS method and measured by volumetric MRI (primary assessor) in EDIT cases with complete MRI acquisition (n=12)

Dotted lines indicate 95% Limits of Agreement

5.3.4.2 Aspiration volume required to detect abnormal P_{EL}

The median volume of fluid aspirated during P_{EL} assessment was 996ml (range 482ml - 2670ml). Abnormal P_{EL} ($MaxP_{EL250} \geq 14.5$ cm H_2O/L) was detected in 7/13 (54%) cases with complete data. In these cases, abnormal P_{EL} was first detected at a median volume of 325ml (range 250ml - 800ml).

5.4 Discussion

5.4.1 Patient preferences in the management of MPE

17/40 potential respondents (43%) completed the TPS. This modest response rate clearly limits the generalisability of the findings, however since all 17 surveyed patients unanimously indicated a preference for first line TSP, it appears that from a patient perspective there remains a significant impetus to further optimise inpatient TSP pathways. The avoidance of long term indwelling prosthetic material was cited as the main reason for choosing TSP over IPC management. Universal IPC management appears unlikely to realistically be able to overcome this patient concern given the length of time required for ambulatory pleurodesis (median time to IPC removal approximately 10 weeks in IPC-PLUS [48]) and this was reflected in the survey findings in that only 4/17 (24%) participants suggested they would consider ambulatory pleurodesis if available. In contrast, the majority of participants (88%) said they found the idea of P_{EL}-directed treatment acceptable, presumably since this represented 'TSP if possible' and would only lead to IPC insertion if TSP was predicted to fail. To build on these findings, a more detailed qualitative exploration of patient preferences from a range of treatment centres is warranted to ensure future treatment developments are appropriately aligned to accommodate the range of patient priorities encountered in this condition.

5.4.1.1 Relationship to previous studies

The findings here are similar to those described by Seymour *et al* in the only comparable study in the current literature. [43] In their similar survey of patient attitudes, over half of patients who indicated a preference for first-line TSP would not consider IPC management, and 80% said they thought ambulatory management would have no effect, or a negative effect, on their quality of life.

5.4.1.2 TSP strengths and limitations

The embedded TPS commenced mid-way through pre-EDIT recruitment. This constrained the available sample size and caution is required in the interpretation of this small-scale single centre survey. Although TSP participants were provided with clear and objective treatment information summaries to read prior to completely the survey, there was clearly significant potential for institutional and investigator bias to influence the participant responses.

Additionally, the majority of respondents had also consented to participation in the full pre-EDIT trial (76%). Pre-EDIT eligibility criteria excluded those with a preference for first-line IPC management and this method of patient selection also clearly limits the generalisability of the survey findings. However, only 3/87 (3%) consecutive patients pre-screened for pre-EDIT participation were excluded on the basis of a clear baseline preference for TSP or IPC.

5.4.2 Performance of M-mode sonography in the detection of NEL

The utility of M-mode sonography as a potential alternative NEL biomarker for use in future trials was explored during the conduct of pre-EDIT. Diagnostic M-mode imaging was obtained in 10/15 EDIT management cases (67%). Two avoidable cases of missing data arose from investigator error during attempts to save the images, however in 3/15 (20%) it was technically impossible to complete an M-mode lung excursion assessment due to either breathing artefact or an inadequate acoustic window. It appears reasonable to assume that similar limitations might be encountered in clinical practice. Although pre-EDIT was not specifically designed to formally compare NEL assessment techniques, the success rate for completing an M-mode assessment encountered here (10/15 (67%)) appears inferior to that of P_{EL} assessment (13/15 (87%), rising to 13/13 (100%) following a software update). Furthermore, the diagnostic performance of M-mode assessment for NEL was poor in the pre-EDIT series with an AUC of only 0.595. Although notable uncertainty exists around the diagnostic performance estimate here, we found no compelling new data to prioritise M-mode sonography over P_{EL} as means of NEL-directed MPE care.

5.4.3 Validation of the definition of P_{EL}

Complete pre- and post-aspiration MRI imaging was obtained in 12 EDIT management subjects. Colleagues from the MR Physics group identified a high level of measurement precision when adopting pre-EDIT imaging protocols and Myrian® software to measure their deformable pleural phantom. Their measurement error was particularly low (0.6%-6.4%) in simulated effusions of volume ≥500ml, which accounted for the majority of pleural cavity volumes measured in pre-EDIT subjects. An extremely high level of inter-observer agreement (ICC > 0.98) was seen between independent MRI assessors which supports the reliability of this novel approach as a gold standard technique to

directly assess the pleural cavity volume. Very close agreement was seen between pleural fluid aspiration volume (V_{OUT}) and directly measured pleural volume (ΔV_{MRI}). This finding validates the indirect definition of P_{EL} ($\Delta IPP/V_{OUT}$) which is widely used in clinical practice.

A slight bias towards V_{OUT} underestimating ΔV_{MRI} was observed. This may have been accounted for by the unavoidable loss of small volumes of pleural fluid during insertion and removal of the DPM catheter. Importantly, it should be noted that none of the 12 EDIT subjects with complete MRI imaging had evidence of post-thoracentesis ex-vacuo pneumothorax. Had his occurred, it may be speculated that transient air ingress into the pleural cavity, either via pleuro-parenchymal fistulation or through instrumentation, would lead to an increase in IPP (and therefore a reduction in ΔIPP) while simultaneously ΔV_{OUT} (and ΔV_{MRI}, if it had been measured) would continue to increase. The net effect may be a trend towards normalisation of P_{EL}. This mechanism may account for some of the discordance seen in a larger observational study between P_{EL} and radiographic NEL, [60] but this hypothesis could not be explored further in this series.

5.4.4 Optimal Aspiration Volume for P_{EL} assessment

In cases where abnormal P_{EL} was present, based on the novel $MaxP_{EL250}$ definition, this was first detected at a median volume of 325ml. The largest volume needed to pass this threshold was 800ml. These findings suggest that the hypothesis stated that a near-maximal fluid aspiration is need for acceptable diagnostic performance is inaccurate. A future elastance-directed pathway may therefore be optimised through the use of more modest aspiration volumes (potentially < 1L) which may in turn improve patient safety (larger residual volume for definitive Seldinger intervention) and convenience (shorter procedure).

5.4.4.1 Use of a TUS effusion volume estimate

Agreement between the Goecke TUS pleural effusion volume estimation and gold standard volumetric MRI assessment was poor in the majority of cases, and grossly inaccurate in 2 cases where the baseline effusion volume exceeded 3L. In hindsight, the inadequacy of V_{TUS} may have been predicted since this method had originally been derived (indirectly from V_{OUT}) from the complete aspiration of a series of effusions only up to 1650ml in volume. [87] The principle limitation

with the Goecke method in larger effusions is likely to relate to the inherent challenge in measuring the lateral height of a pleural effusion beyond the level of the axilla due to loss of acoustic access. This weakness in the Goecke TUS effusion volume estimate only became apparent early in the conduct of pre-EDIT. As described in Chapter 4, section 4.3.3.3, it was clinically apparent that this method risked unnecessary early termination of pleural aspiration in cases with a large initial effusion thus potentially compromising the sensitivity of P_{EL} assessment. The trial protocol was amended after the delivery of 2 episodes of EDIT management to allow the use of a mid-procedure assessment of residual effusion volume to guide the stop point for P_{EL} assessment (aspiration terminated when horizontal lung-costal pleural distance $\leq$ 30mm). The original versions of the protocol had sought to provide maximal objectivity at each step of the pathway, hence the use of a pre-set maximum aspiration target, and reduce the need for the additional complexity of mid-procedure TUS assessments. However, this strategy was clearly unsuccessful. The experience of the amended method utilising a mid-procedure TUS assessment was positive from an operator perspective and arguably better reflects the real-time decision making required in clinical practice. The replacement of a pre-specified TUS-based target aspiration volume with regular mid-procedure TUS assessment therefore represents a logical refinement to the EDIT pathway.

5.4.5 Conclusions

This chapter has generated a number of important findings that will be incorporated into future studies, including a definite Phase III trial of EDIT management. The embedded TPS within pre-EDIT has provided a valuable insight into patient preferences in the management of symptomatic MPE. Although caution must be taken not to overinterpret these findings, there appears to be at least some degree of appetite from a patient perspective to further refine TSP pathways. In that regard, the findings from pre-EDIT support the development of P_{EL}-directed therapy. In addition, novel volumetric MRI data obtained here validates the widely adopted clinical 'indirect' definition of P_{EL} ($\Delta IPP/V_{OUT}$), at least in those cases without ex-vacuo pneumothorax. The aspiration volume required to detect abnormal P_{EL} where present, may be more modest than we hypothesised ($\leq$ 800ml in all EDIT cases with NEL) making a less than near-maximal aspiration a feasible option within a future larger EDIT trial.

However, the Goecke TUS method was demonstrated to be inaccurate, especially in larger effusions, and is therefore not suitable for computation of a target aspiration volume in future studies.

Chapter 6

CONCLUSIONS

6 Chapter 6: Conclusions

The management of Malignant Pleural Effusion has evolved significantly in recent years, however Non-expansile Lung remains a prominent, but poorly defined and often occult, obstacle to effective palliation in a significant proportion of patients. Indwelling pleural catheters have led to a paradigm shift in the management of MPE and are increasingly recognised as a first-line definitive intervention in preference to talc slurry pleurodesis. However, IPCs are not universally acceptable to patients and come with important disadvantages, costs and risks. Therefore, the development of a robust and efficient treatment pathway for patients wishing to avoid indwelling prosthetic material, remains a clinical imperative.

The initial observational work in this thesis has contributed to our understanding of the prevalence of NEL in MPE, the prognostic significance of this finding and the limitations of its radiographic detection. The challenges reported in Chapter 3 in reliably detecting NEL strongly motivated our unit to use pleural manometry to develop of a stratified treatment pathway designed to reduce pleurodesis failure, moving away from use of P_{EL} as way of detecting NEL *per se*. The subsequent pre-EDIT feasibility RCT (reported in Chapters 4 and 5) has greatly enhanced our knowledge of how such a goal may be delivered and facilitated evidence- and experience-based refinements to the design of a proposed future phase III study of EDIT management (the EDIT trial).

6.1 Post-drainage radiographic identification of non-expansile lung and its prognostic significance

In this multicentre observational study, the proportion of patients with NEL (defined here as less than 50% pleural apposition) in a cohort of patients with MPE undergoing LAT was high (17–34%). This definition identified gross radiographic NEL which would preclude an attempt at TSP. The high prevalence of NEL encountered suggests that NEL is under-represented in important landmark trials of IPC-based MPE management such as TIME-2 (6% NEL) and AMPLE (3% NEL). [2,3] As such, clinical equipoise between IPC and TSP for all patients with MPE cannot be assumed, and refinements to TSP pathways are required.

Radiographic identification of NEL was subject to a high level of inter-observer variation. NEL was associated with adverse survival in both retrospective cohorts studied. However, the independence of this relationship was not externally validated, probably due to a type II statistical error and the potential for misclassification of borderline cases given the limitation of single-observer radiographic classification. In the analysis of 'extreme expansion phenotypes', the possibility of misclassification was eliminated and this work supports the hypothesis that there is a genuine prognostic disadvantage associated with NEL.

The findings from this study should be considered in clinical practice. In cases with borderline NEL, the opinion of a second observer (and even a third, in the event of disagreement) may be justified to improve the consistency of clinical decision-making. Furthermore, the results are pertinent to the design and conduct of future MPE trial design which should seek to identify NEL biomarkers which are associated with less inter-observer variation. As previously discussed, the ideal biomarker would allow reliable detection of NEL at an early stage prior to complete effusion drainage thereby creating the potential to improve patient outcomes through the avoidance of futile TSP attempts.

6.2 Feasibility of a randomised controlled trial of elastance-directed management in malignant pleural effusion

6.2.1 Recruitment and technical feasibility

Pre-EDIT was the first randomised controlled trial in which pleural management was directly guided by pleural manometry data. The successful conduct of the trial has shown that it is feasible to recruit patients with symptomatic MPE to an RCT of an elastance-directed treatment pathway in sufficient numbers (31 patients over 55 weeks from a single centre) to justify progressing to an appropriately powered multicentre trial of efficacy of such a pathway. Importantly, EDIT management was also safe (no directly related SAEs) and technically deliverable (complete P_{EL} assessment and delivery of per-protocol definitive intervention in 13/13 (100%) after an early DPM software update). EDIT management was also time efficient; in all EDIT cases, a definitive intervention was delivered within 24 hours of P_{EL} assessment, with only 1/15 (7%) requiring the use of pneumothorax induction due to insufficient residual

fluid. In pre-EDIT, the (MRI-incompatible) manometry catheter had to be removed before placement of the elastance-directed treatment (IPC or ICD). However, in future research, and ultimately clinical practice, a guidewire could simply be placed through the lumen of the manometry catheter facilitating immediate replacement for an IPC or ICD, thereby further improving the efficiency the pathway, and likely completely negating the need for pneumothorax induction.

6.2.2 Diagnostic performance of P_{EL}

Although pre-EDIT included insufficient cases to comment on clinically defined treatment success rates (e.g. at 3 month follow-up), a *post-hoc* analysis reassuringly identified that $MaxP_{EL250}$ detected NEL with a high degree of sensitivity (100% (95% CI 51-100%)) and an acceptable level of specificity (67% (95% CI 35-88%)). These estimates of diagnostic performance are necessarily associated with wide confidence intervals given the small sample size, but nonetheless support the use of $MaxP_{EL250} \geq 14.5$ cm H_2O/L as a NEL biomarker in future research into elastance-directed therapy.

6.3 Optimisation of an elastance-directed management pathway for malignant pleural effusion

6.3.1 Treatment preferences

The conduct of pre-EDIT provided an invaluable opportunity to refine the EDIT management pathway and ensure it was aligned with patient treatment preferences and priorities. The patient survey embedded within pre-EDIT, identified a strong preference for inpatient TSP over first-line IPC insertion. The generalisability of the TPS findings may have been limited by patient selection as the majority of respondents (13/17 (76%)) were full pre-EDIT participants and had opted not to have a first-line IPC. However, since only 3% of those pre-screened for pre-EDIT were excluded on the basis of treatment preference, the magnitude of any patient selection bias should be low. The avoidance of 'long term' indwelling prosthetic material (assuming TSP success) was the most common reason for choosing first-line TSP (53% of respondents). When presented with hypothetical alternative management strategies, the addition of a pleural elastance assessment was considered acceptable by 88%, whereas only 24%

indicated they would choose ambulatory pleurodesis over TSP if both options were available. While obviously limited by selection bias, as discussed, and a small sample size, these findings are supportive of efforts to improve the success of inpatient TSP using P_{EL} as a NEL biomarker.

6.3.2 Choice of NEL biomarker

M-mode sonographic assessment of atelectatic lung has been described as a potentially widely deployable non-invasive biomarker of NEL. It was therefore logical to evaluate this technique in parallel with P_{EL} within pre-EDIT. M-mode acquisition was hampered by poor reliability (20% technical failure rate) and poor diagnostic performance (area under ROC curve 0.595). There was therefore no new data recorded to support a shift away from P_{EL} to M-mode TUS for detection of NEL. Additionally, volumetric MRI data from 12 EDIT patients with complete imaging validated the clinical definition of P_{EL} ($\Delta IPP/V_{OUT}$) in patients without post-thoracentesis NEL, and lends further weight to the development of P_{EL} as a clinical biomarker.

6.3.3 P_{EL} assessment aspiration volume

Using the novel $MaxP_{EL250}$ definition to identify NEL, only a modest aspiration volume (median 325ml, range 250ml - 800ml) was required to detect abnormal physiology. Large aspiration volumes (> 1.5L) in excess of BTS guidelines therefore appear unnecessary to reliably detect NEL. Furthermore, the Goecke effusion estimation used initially to guide the maximal aspiration volume in pre-EDIT was inaccurate. This was swiftly replaced (after 2 EDIT cases) with a real-time TUS assessment which was more akin to routine clinical decision making. This streamlined method was associated with a positive operator experience and, importantly, achieved a high sensitivity for NEL detection (100%) achieved. This experience suggests mid-procedure TUS should be integrated into future iterations of EDIT management.

Finally, assuming the Rocket Medical DPM equipment can be suitably adapted to provide real-time elastance data, then P_{EL} assessment could also be terminated as soon as an abnormal P_{EL250} value is identified. Ideally, this process would be fully automated by integrating real-time flow measurement into the DPM system, but in the shorter term could probably be achieved with a software

update to allow the operator to manually record the removal of each 50ml aspiration aliquot during the procedure.

6.4 Future work

The work presented in this thesis has ultimately informed the design of the proposed ‘EDIT trial’, a phase III study of the efficacy of EDIT management. The experience and data gathered from each aspect of the pre-EDIT trial has been used to refine and optimise the EDIT trial protocol; a proposed trial synopsis is presented in Appendix 10. Funding for the EDIT trial has been secured at the time of publication of this thesis and recruitment is expected to commence in Q3/4 2021.

Appendix 1 Pre-EDIT study patient information sheet

Acute Services Division

Regional Services Directorate

NHS Greater Glasgow and Clyde

INFORMATION SHEET FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project:

Pre-EDIT: A randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc Pleurodesis (EDIT) in the management of symptomatic Malignant Pleural Effusion without obvious non-expansile lung

Invitation Paragraph

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of the study?

A pleural effusion is a collection of fluid inside the chest. The fluid gathers in space called the pleural space which lies between the lung and the rib-cage. This often causes breathlessness and may unfortunately be caused by cancers affecting the pleural lining. This is called a 'Malignant Pleural Effusion'. The current standard treatment for this involves admitting the patient to hospital and draining the fluid over several days using a small chest tube (or 'drain'). Ideally, this allows the lung to re-expand into its normal position against the rib-cage. We can then put medical talc powder into the chest by flushing it down the chest drain which was used to empty the fluid. This talc acts like a glue and sticks the lung against the rib-cage, preventing any fluid from coming back – this process known as talc pleurodesis. In about 1 in 5 patients, talc pleurodesis fails because the lung does not re-inflate fully after fluid has been drained. This is called 'non-expansile lung'. In this situation the fluid almost always comes back.

If doctors could identify which patients had non-expansile lung at the start, they could avoid these failures and use a different method to treat these patients. IPCs (indwelling pleural catheters) are very effective at improving breathlessness in patients with non-expansile lung. However they require a different kind of chest drain and this needs to be left in the chest, often for many months. Via the IPC, fluid can be drained at home by the patient's district nurse, who needs to be trained in the technique. Insertion of an IPC therefore requires some planning and they are not suitable for all patients. Currently, doctors find it very difficult to predict which patients will have non-expansile lung and a significant number of patients will therefore have an attempt at talc pleurodesis without success. These patients are therefore exposed to the risks of the procedure and several days in hospital without any benefit.

We plan to test a new approach which involves measuring something called 'elastance' inside pleural space before a decision is made to try Talc Pleurodesis. Elastance reflects the ability of the lung to re-expand after fluid is withdrawn. Based on previous studies we think measuring elastance will allows us to accurately identify patients with non-expansile lung who should not be offered talc pleurodesis. We can then offer these patients insertion of an IPC instead and avoid a week in hospital and the small risks of Talc Pleurodesis. This new approach is called 'EDIT management'.

As part of EDIT management we will perform an additional local anaesthetic procedure to drain off some pleural fluid and measure elastance before making a decision between talc pleurodesis and insertion of an IPC. The device we will use to measure elastance has been fully safety tested and approved for use in people. It has therefore been given a 'CE mark' for this purpose; however it has not been used to direct management of patients before. For us to prove whether EDIT management using this new device improves the management of patients with malignant pleural effusion we will need to perform a large study, involving several hundred patients. The purpose of this study (called the pre-EDIT study) is to assess whether our proposed study methods are acceptable to patients and to gather information which will help us design the future EDIT study properly.

Ultimately, we hope EDIT treatment will mean patients will get the most useful procedure first time and avoid the risks and time in hospital caused by procedures which were not successful.

Why have I been invited to take part?

You have been invited to take part in this study because you have a collection of fluid in the chest (pleural effusion). Your doctors will have already explained that this has unfortunately been caused by cancer (a malignant pleural effusion). Your doctors will also have explained that your breathing is likely to be improved by drainage of the fluid, but that fluid will likely recollect unless an additional procedure is performed to stop this. As mentioned earlier the standard approach in this situation is to attempt a talc pleurodesis and you are therefore eligible for this study.

Do I have to take part?

No, it is up to you to decide whether or not to take part. We will talk you through the study and go through this information sheet, which we will then give to you to keep. If you decide to take part, you will be asked to sign a consent form to show you have agreed to take part. If you decide to take part, you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive or your future treatment.

What will happen to me if I decide to take part?

If you are interested in taking part in the study, we will first arrange a 'screening visit'. The purpose of this visit is to check that the study would definitely be suitable for you. We will ask you to sign a consent form before arranging this appointment, which does not commit you to anything else.

If you are an inpatient one of the team will come to see you in your ward. During the screening visit, the research doctor will perform an ultrasound scan of your chest to estimate how much fluid you have around your lung. This is a scan you will have had before as part of your normal care; it painless and does not involve any risk. To be in the study, there needs to be a certain amount of fluid in your chest. The doctor will also run through a short list of questions to be sure you can be included. If you are eligible, the process of the study will be described to you in detail and you will have to opportunity to ask questions and think about whether you wish to be involved. If you want to go ahead, the doctor will ask you to sign a second consent form for enrolment into the study.

We will then arrange for you to be admitted to ward 7B at the Queen Elizabeth University Hospital. This ward specialises in treating patients with problems relating to fluid around the lungs. If you are in hospital in another ward, we can easily make arrangements for you to be transferred to ward 7B. On the ward, one of the research doctors or nurses will go through a questionnaire with you to collect details about your symptoms. They will also record some details about your medical history and test results from your hospital notes.

The pre-EDIT study (and the EDIT study which will follow it) is a 'randomised' study. This allows the research team to compare what happens to patients treated in two different ways. In this case the comparison is between 'EDIT management' and 'standard care'. The next step in the study process is therefore to randomise you between the two approaches

(known as 'arms'). At this point it is important to remember that the treatment in both 'arms' will be carried out by the same people, i.e. the clinical team you already know. 'Standard Care' is the normal approach used in all patients not in the study and is the current best way to do things. 'EDIT management' is the new method, which we think may be better, but have no proof of this at present. The fact that there is genuine uncertainty about which is better makes 'randomisation' between the two approaches the right thing to do.

To perform the randomisation we will use a simple computer system. This ensures that half of the people in the study will have their effusion treated in the usual way (Standard Care) and the other half will be treated using the new method (EDIT treatment). All patients in the study will have their treatment delivered by the same team of doctors and nurses, all of whom specialise in these problems.

What happens next will depend on whether you have been allocated to 'Standard Care' or 'EDIT treatment'

- In patients receiving 'Standard Care' a chest drain will be inserted using local anaesthetic to ensure you are comfortable throughout this. All of the fluid will be drained over the next few days on the ward. If the lung re-expands then medical talc will be flushed down the chest drain to prevent the fluid from coming back (i.e. a talc pleurodesis will be performed if possible). If the lung does not fully re-expand after the fluid has been drained the drain will be removed and you will be able to go home. You will then be followed up carefully in the clinic.
- In patients receiving 'EDIT treatment', pleural elastance will be measured before any decision is made to try a talc pleurodesis. This will be done during an additional fluid drainage procedure using local anaesthetic to ensure you are comfortable. After this, the doctor will use the elastance measurements to work out whether or not your lung is likely to re-expand after fluid is drained. If it is likely to re-expand, they will then insert a standard chest drain and attempt a talc pleurodesis (like all of the patients receiving 'Standard Care'). However, if your lung is not likely to re-expand based on the elastance measurements, they will insert an indwelling pleural catheter (IPC) as described earlier. If you have an IPC inserted you will go home as soon as you are comfortable with this device (usually the next day).

  Patients receiving 'EDIT treatment' will also have an MRI scan before and after elastance measurements are made. This is to allow us to check that the ultrasound measurements made during the screening visit are accurate and the elastance measurements made were correctly calculated using the new device.

For patients receiving 'Standard Care' we would expect you to stay in hospital for 5-7 days. We expect that most patients receiving 'EDIT treatment' will stay in for a similar length of time, but those treated with an IPC will probably go home much sooner, probably the following day.

We would like to see all patients back for a follow-up visit to see how they are doing. We will collect details on your symptoms and whether or not you have needed any further treatment for pleural effusion. Wherever possible, we will arrange this to fit in with one of your routine hospital follow-up appointments. You will also be asked to record some pain and breathlessness questionnaires once per week for 4 weeks once you have gone home.

What do the MRI scans involve?

The MRI scans will be performed at the Glasgow Research Imaging Facility at the Queen Elizabeth University Hospital. The first scan should take no more than 45 minutes and the second one will be much shorter, approximately 20 minutes.

On arrival at the MRI department a radiographer will go through a safety checklist and make sure that all magnetic objects (e.g. jewellery and bankcards) have been removed. Following this you will be asked to complete and sign a safety questionnaire. If there is felt to be a risk of small metal fragments in your eyes based on previous work or hobbies you may also need to have an xray to exclude these prior to having the MRI scan. The amount of radiation involved in this xray is minimal and considered completely safe.

You will be given a hospital gown to change into and then asked to lie flat on an electric bed that will move you into the scanner. The scanner is basically long and tunnel shaped. You are gently slid into the centre of the tunnel on a moving bed and the scan pictures are taken. Some people find it a little enclosing, but you can come out at any time. If you are claustrophobic please tell staff.

When you are in the scanner you will need to wear a pair of headphones, allowing you to listen to music of your choice (you are welcome to bring your own CD) and allowing us to communicate with you. The headphones are also necessary because of the loud knocking noise that occurs when the pictures are being taken. You will be given an emergency buzzer and can very quickly be taken out of the scanner should you feel uncomfortable or if it is felt necessary. During the scan you will be asked to hold your breath at times (to give a crisp picture) and to take some deep breaths in and out (so we can see how much your lung moves whilst the fluid is still there). A doctor will be in the control room throughout this procedure.

What are the possible benefits of taking part?

It is possible that those patients who receive EDIT treatment will be less likely to have failed treatment and need further procedures. However, it is important to stress that this is not yet proven and will need tested in a larger study (the EDIT study) if the current study (pre-EDIT) shows promising results.

Even if we don't find that the EDIT treatment works well, it will give researchers extremely useful information which may help guide future treatments and help us to know how they should be tested. This may be of benefit to other patients in the future.

What are the potential risks in taking part?

There are risks with all medical procedures, including those given as part of 'Standard Care', but the chances of a serious complication are low. National guidelines will be followed to minimise risk. All procedures will be performed by a suitably trained and experienced doctor.

The particular risks will be explained to you before each procedure and you will have chance to ask as many questions as you wish before proceeding. All chest drainage procedures carry small risks including discomfort (although once local anaesthetic is given, we expect all patients to be comfortable during these procedures), bleeding, infection, damage to the lung or other structures in the body, failure to complete the procedure and risk of any drain inserted becoming dislodged before the talc is given. IPCs carry the same risks, although the risk of infection is higher (5-10%, over the time in which the IPC is kept in). This higher infection risk is worth it because an IPC is the only effective treatment for patients in whom a talc pleurodesis fails.

It is important for you to understand that patients who receive EDIT treatment will have an additional fluid drainage procedure to allow elastance measurements to be taken. In order to get these measurements, this procedure might involve removal of a larger volume of fluid that is normally recommended in 'routine practice'. However, 'routine practice' does not involve use of pressure monitoring during fluid drainage, which we plan to do in this study. This is important because drainage of large volumes has been shown to be safe when pressure monitoring is used. Therefore, we do not believe this will involve any significant additional risk. Having two procedures rather than just one may increase the risk

of a complication since each procedure has its own risks, but as mentioned before, the size of these risks are very low.

EDIT treatment patients will also have less fluid in their chest when their chest drain or IPC is inserted (after making this decision based on elastance results). This may mean that a slightly different technique is needed to put the drain in safely without causing damage to the lung underneath. This would involve use of blunt needle to let a small amount of air into the chest before the drain goes in. This ensures that the lung is not close to the rib cage when the drain is inserted. This technique is used every week to perform similar procedures in our unit and across the country. It is considered a safe way to perform procedures in this setting and we do not think this significantly increases any risks. However this will be carefully recorded during the study.

Are there any risks related to the MRI scans?

The MRI scanner is very safe as long as you have no metal implants in your body. Staff who are experienced in MRI scans will be present during your MRI scan and you will be asked a series of safety questions to ensure you have no metal implants/fragment in your body. If you do have a metal implant/fragment an MRI scan may not be safe and you would not be eligible for this study.

During the MRI scan a dye (contrast agent) will be injected into a vein in your arm. This makes any abnormal tissue appear brighter on the scan and easier to measure. The dye is called Gadolinium DTPA and is generally very safe. There are however some potential side effects although these are uncommon and generally mild. The most frequent side effects are a brief headache and nausea (feeling sick). This occurs in 1 to 3 patients out of every hundred who have the injection. Sometimes there is a sensation of heat, cold and/or pain at the injection site. An extremely rare (affecting less than 1 in 10000 people receiving Gadlinium), but serious, side effect is an allergic reaction to the dye therefore please inform the doctor if you have a history of allergies. This type of reaction may involve difficulty breathing and swelling of the lips or face but generally responds very well to emergency drug treatment.

Gadolinium contrast can also very rarely cause a serious condition called nephrogenic systemic fibrosis (NSF) in patients who have very poor kidney function. Your doctor will check blood tests to measure your kidney function as part of your routine care and will inform you if your kidney function is not good enough for the Gadolinium to be given safely with regards to this rare complication. In patients with normal kidney function the Gadolinium is cleared from the body in the urine within 24 hours and NSF is not a concern.

Are there risks from the X-rays in the study?

During the course of the study you will need to have approximately 8 chest x-rays. As mentioned above, you may also need to have 2 x-rays of the eyes to exclude metal objects before having an MRI scan. X-rays involve exposing the body to radiation which can be harmful at high levels but the total dose of radiation involved in this study is extremely low. It is equivalent to the same amount of radiation a typical person would receive from their normal surroundings over a period of 16 days and is therefore considered to be trivial by radiation experts.

What if something goes wrong?

If you have a concern about any aspect of this study, you should ask to speak with the research doctor/nurse who will do their best to answer your questions.

If taking part in this research study harms you, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay your legal costs. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanism is available to you.

If you have private medical insurance, you may wish to check with your company before agreeing to take part in the study to ensure that participation in the study will not affect your insurance cover.

Will my taking part in the study be kept confidential?
You can be assured that any data collected during the course of this study and any of the results published will not identify you personally. Your medical records will only be available to the research doctors, your hospital consultant, trial sponsor (NHS Greater Glasgow & Clyde) and regulatory authorities.

We will inform your general practitioner (GP) of your participation in this study.

We would like to use your NHS number to follow-up on your health.

Data Transparency Statements
NHS Greater Glasgow & Clyde is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. NHS Greater Glasgow & Clyde will keep identifiable information about you for 10 years after the study has finished. Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible. You can find out more about how we use your information by contacting the study team (see details below).

The research team will use your name, CHI number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from NHS Greater Glasgow & Clyde and regulatory organisations may look at your medical and research records to check the accuracy of the research study. The study team will pass these details to NHS Greater Glasgow & Clyde along with the information collected from you and your medical records. The only people in NHS Greater Glasgow & Clyde who will have access to information that identifies you will be people who need to contact you to coordinate follow-up or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, CHI number or contact details. The study team will keep identifiable information about you from this study for 10 years after the study has finished.

NHS Greater Glasgow & Clyde will collect information about you for this research study from your electronic medical records. This information will include your name, CHI number, contact details and health information, which is regarded as a special category of information. We will use this information to anonymously describe the group of patients included in the study and look for connections between the study findings and participants past medical history.

Who is organising and funding the research?
The research is being carried out by Dr. Kevin Blyth from the Department of Respiratory Medicine at the Queen Elizabeth University Hospital, Glasgow.

The costs of running and organising this study have been met by a grant from the NHS Greater Glasgow & Clyde Endowment Fund and Rocket Medical. None of the doctors or other staff conducting the research are being paid for recruiting patients into the study.

Who has reviewed the study?

This study was reviewed by a number of medical specialists during its development. All research in the NHS is also looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. The West of Scotland Research Ethics Committee has reviewed and approved this study to confirm that the 'rights and protection of patients' health have been considered. In addition, the study has been reviewed by the Research and Development Department of your local hospital.

Contact for further information

If you have further questions about your illness or clinical studies, please discuss them with your doctor. If you would like independent advice or further information you may also find it useful to contact British Lung Foundation, website: www.blf.org.uk, telephone 03000 030 555 and address: British Lung Foundation, 73-75 Goswell Road, London, EC1V 7ER

If during the course of the study you have any questions regarding your participation or would like further study specific information before making your decision please contact:

Name	**Dr Kevin Blyth**
Telephone Number	**0141 451 6099**

If you find the wording difficult to understand or would like us to explain things to you once more, please feel free to ask your doctor, or nurse.

Thank you for taking the time to read this information sheet. If you wish to take part you will be given a copy of this information sheet and a signed consent form to keep.

Appendix 2 Treatment Preferences Survey patient information sheet

Acute Services Division

Regional Services Directorate

NHS Greater Glasgow and Clyde

PATIENT PREFERENCE SURVEY FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT

Title of Project:

Pre-EDIT study: Survey of Patient Treatment Preferences for Symptomatic Malignant Pleural Effusion

Invitation Paragraph

We would like to invite you to take part in a short treatment preference survey which is connected to a research study called Pre-EDIT. It should only take about 2 minutes to complete. Your answers to this survey will be anonymised and will have no bearing on your medical care. Participating in this survey is separate to the Pre-EDIT study and does not commit you to any other research activity.

Please take time to read the following information carefully. Talk to others about the survey if you wish. Ask us if there is anything that is not clear or if you would like more information.

What is the purpose of this survey?

A pleural effusion is a collection of fluid inside the chest. The fluid gathers in an area called the pleural space which lies between the lung and the rib-cage. This often causes breathlessness and may unfortunately be caused by cancers affecting the pleural lining. This is called a 'Malignant Pleural Effusion'.

There are currently 2 main ways for doctors to treat Malignant Pleural Effusion. These are called 'talc pleurodesis' or 'IPC insertion' and are described in more detail at the beginning of the survey. Both are effective treatments but both have their own advantages and disadvantages. Individual patient preference is therefore essential in deciding the best treatment.

We would like to better understand the views of patients in making a decision between talc pleurodesis and IPC insertion. In particular, we would like to know which pros and cons of the two treatments are deemed most important. This will allow us to direct our research efforts to focus on improvements to these treatments which are most relevant to our patients.

Why have I been invited to take part?

You have been invited to take part in this study because you have a pleural effusion causing breathlessness and your doctors have recommended either talc pleurodesis or IPC insertion.

Do I have to take part?

No, it is entirely up to you to decide whether or not to take part. We will talk you through the survey and go through this information sheet, which we will then give to you to keep. If you decide to take part, you will be asked to sign a consent form to show you have agreed to take part. If you decide to take part, you are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive or your future treatment.

What are the possible benefits of taking part?

Completing this survey will not have any direct benefits to your own medical care but we hope this information will be of benefit to patients in the future by directing our research towards

improving our treatments in a way that matters to patients. We also hope the results will better inform the way in which doctors discuss these treatments with patients.

What are the potential risks in taking part?
There are no risks associated with completing this survey. Your answers will have no bearing on your medical care.

Will my taking part in the study be kept confidential?
You can be assured that any data collected during the course of this survey and any of the results published will not identify you personally. We may use anonymised quotes from your responses in our report of the survey results and any possible publications that arise from this.

Who is organising and funding the research?
The research is being carried out by Dr Kevin Blyth from the Department of Respiratory Medicine at the Queen Elizabeth University Hospital, Glasgow.

The costs of running and organising the Pre-EDIT study, which this survey is part of, have been met by a grant from the NHS Greater Glasgow & Clyde Endowment Fund and Rocket Medical. None of the doctors or other staff conducting the research are being paid for recruiting patients into the survey.

Who has reviewed the study?
This study was reviewed by a number of medical specialists during its development. All research in the NHS is also looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. The West of Scotland Research Ethics Committee has reviewed and approved this study and survey to confirm that the 'rights and protection of patients' health have been considered. In addition, the study has been reviewed by the Research and Development Department of your local hospital.

Contact for further information
If you have further questions about your illness or clinical studies, please discuss them with your doctor. If you would like independent advice or further information you may also find it useful to contact British Lung Foundation, website: www.blf.org.uk, telephone 03000 030 555 and address: British Lung Foundation, 73-75 Goswell Road, London, EC1V 7ER

If during the course of the study you have any questions regarding your participation or would like further study specific information before making your decision please contact:

Name	**Dr Kevin Blyth**
Telephone Number	**0141 451 6099**

If you find the wording difficult to understand or would like us to explain things to you once more, please feel free to ask your doctor, or nurse.

Thank you for taking the time to read this information sheet. If you wish to take part you will be given a copy of this information sheet and a signed consent form to keep.

Appendix 3 Pre-EDIT screening visit consent form

CONSENT FORM FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT:

CONSENT TO PRE-EDIT STUDY **SCREENING VISIT**

Title of Project: Pre-EDIT: A randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc Pleurodesis (EDIT) in the management of symptomatic Malignant Pleural Effusion without obvious non-expansile lung

Please initial EACH BOX

1. I confirm that I have read and understand the information sheet dated …… (Version ……) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I agree to attend for a study screening visit, including chest ultrasound scan, as described in the Patient Information Sheet. ☐

Please sign and date below:

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix 4 Pre-EDIT study consent form

CONSENT FORM FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT:

CONSENT TO **PARTICIPATION IN PRE-EDIT STUDY**

Title of Project: Pre-EDIT: A randomised, feasibility trial of Elastance-Directed Intra-pleural catheter or Talc Pleurodesis (EDIT) in the management of symptomatic Malignant Pleural Effusion without obvious non-expansile lung

Please initial EACH BOX

1. I confirm that I have read and understand the information sheet dated …… (Version ……) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand the study involves random allocation of treatment which neither myself nor the researchers can influence. ☐
4. I understand I may be asked to have two MRI scans for research purposes and understand and accept the possible risks from these. ☐
5. I agree to the recording of my measurements, including elastance measurements, volume of fluid removed and MRI scan findings as described in the Patient Information Sheet. ☐
6. I agree to the recording of my pain and breathlessness scores as described in the Patient Information Sheet ☐
7. I give permission for my initials, date of birth and NHS or Community Health Index (CHI) number to be collected for follow-up purposes. ☐
8. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from NHS Greater Glasgow and Clyde (study sponsor) or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐
9. I consent to my GP being informed of my participation in this study. ☐
10. I agree to take part in the above study. ☐

Please sign and date below:

----------	----------	----------
Name of Participant	Date	Signature
----------	----------	----------
Name of Researcher	Date	Signature

Appendix 5 Treatment Preferences Survey consent form

CONSENT FORM FOR PATIENTS/ VOLUNTEERS IN CLINICAL RESEARCH PROJECT:

CONSENT TO PRE-EDIT TREATMENT PREFERENCE SURVEY

Title of Project: Pre-EDIT study: Survey of Patient Treatment Preferences for Symptomatic Malignant Pleural Effusion

Please initial EACH BOX

1. I confirm that I have read and understand the information sheet dated …… (Version ……) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand my responses will be anonymised for the purpose of analysing the survey and reporting its findings but that anonymised quotes may be used in publications. ☐
4. I agree to my anonymised responses being stored on secure NHS computer systems. ☐
5. I agree to participate in the above survey. ☐

Please sign and date below:

Name of Participant	Date	Signature
Name of Researcher	Date	Signature

Appendix 6 Pre-EDIT embedded Treatment Preferences Survey

Pre-EDIT Study: Survey of Patient Treatment Preferences for Symptomatic Malignant Pleural Effusion

Introduction

Thank you for agreeing to take part in this survey of treatment preferences. Please read the treatment summary below before answering the questions on the following page. If there is anything you do not understand, please ask the research doctor or nurse for more information.

Treatment Information Summary

There are currently 2 main ways to treat breathlessness caused by a Malignant Pleural Effusion. These are called 'talc pleurodesis' and 'IPC insertion'. IPC stands for Indwelling Pleural Catheter. Both are effective treatments and your doctors will have discussed these options with you. We have provided some written information about the advantages and disadvantages of each and are keen to learn more about the factors involved in the treatment decision you have made.

Talc Pleurodesis

Talc pleurodesis involves draining all of the fluid out of your chest using a small plastic tube called a chest drain. X-rays are used to assess whether the lung has re-expanded and made contact with the ribcage. Once this happens, sterile medical talcum powder (talc) is flushed down the chest drain and acts as a glue to fuse the lung surface to the ribcage. The drain is then removed. This process takes several days and requires an admission to hospital (for an average of 4-7 days). Talc Pleurodesis is successful in about 70% of people, in that it prevents the fluid from building up again and further procedures are not required.

One of the main problems with talc pleurodesis is that the lung does not fully inflate after fluid is drained in about 1 in 4 patients. This means that lung cannot be glued to the ribcage and in many patients the fluid will come back and a further drain will be required. Importantly, we cannot currently tell you before draining the fluid whether your lung will reinflate or not. This means 1 in 4 patients spend several days in hospital but do not get any talc put into their chest.

IPC Insertion

An IPC, or Indwelling Pleural Catheter, is a type of soft plastic drain which is tunnelled under the skin and can be drained at home by district nurses or a family member. Between drainages it is covered by a discrete dressing and is not attached to anything. IPCs can help your breathing even if your lung does not re-inflate after fluid is removed. They can be inserted as a day case under local anaesthetic, meaning a stay in hospital is not required.

The main drawback is that the drain needs to stay in for a long time, often indefinitely. Although in about 4 out of 10 patients, their IPC can be removed at some point as the fluid dries up. Some patients find an IPC inconvenient as it can interfere with daily activities such as swimming or bathing. Others do not like the hassle of a tube, or having a daily reminder of their illness. IPCs can also get infected. Because the drain is in for longer this risk is higher than for talc pleurodesis drains. Usually, infection can be treated without removing the IPC but this may require a lengthy hospital admission and prolonged antibiotics.

Table summarising the pros and cons of Talc Pleurodesis vs IPC Insertion

	Talc Pleurodesis	IPC Insertion
FOR	Lower risk of infection	Can be inserted as day case (or 1 night stay)
	If it works, there is no need for long term drain	May improve breathlessness if your lung doesn't re-expand after fluid drainage
AGAINST	Requires 4-7 day stay in hospital	Higher risk of infection (5-10%)
	The lung needs to reinflate for it to work (will not happen in around 1 in 4 patients)	Care of drain site required and a 'reminder' of illness

Pre-EDIT TPS _ _ _
Pre-EDIT study ID (if applicable) _ _ _ Patient initials _ _ Date completed __ /__ /____

SURVEY QUESTIONS

1. **Having discussed the options with your doctor, read the attached information and had the opportunity to ask questions, do you think you have enough information to make a decision about your treatment?**
   Please tick one box

   Yes ☐
   No ☐

2. **Which of the following would you prefer to treat your malignant pleural effusion?**
   Please tick one box

   Talc Pleurodesis ☐
   IPC Insertion ☐ } ***go to question 3***

   I would be happy to have either ☐
   I'm still not sure ☐ } ***go to question 4***

3. **What was the main reason for choosing this treatment?**
   Please circle the single most important reason in the table below

	Talc Pleurodesis	IPC Insertion
FOR	Lower risk of infection	Can be inserted as day case (or 1 night stay)
	If it works, there is no need for long term drain	May improve breathlessness if your lung doesn't re-expand after fluid drainage
AGAINST	Requires 4-7 day stay in hospital	Higher risk of infection (5-10%)
	The lung needs to reinflate for it to work (will not happen in around 1 in 4 patients)	Care of drain site required and a 'reminder' of illness

   Or if there is another reason for your answer not in the table, please write this in the box below:

4. **If you would be happy to have either treatment or still aren't sure which to choose, please write down which advantage or disadvantage you think is most important.**
   Please write in the box below

Pre-EDIT TPS _ _ _
Pre-EDIT study ID (if applicable) _ _ _ Patient initials _ _ Date completed __ /__ /____

4. **In the future, doctors may be able to routinely put talc 'glue' down an IPC. Research suggests that this would probably mean that about 5 out of 10 patients would be able to have their IPC removed after 10 weeks and not require any more procedures. If you answered 'Talc Pleurodesis' for question 1.a), would having this option available make you more likely to choose an IPC?**
Please tick one box

Yes, I would change my mind and choose IPC Insertion ☐
No, I would still prefer Talc Pleurodesis ☐
Not applicable, IPC Insertion is already my first choice ☐

5. **In the Pre-EDIT study we are researching the possibility of performing an extra fluid drainage procedure to take some pressure measurements from the chest before deciding which treatment (either Talc Pleurodesis or IPC) might be best. The reason for this is that if the pressure measurements show the lung will not re-expand then we think Talc Pleurodesis is far less likely to be successful and we would not recommend trying it. If the pressure measurements suggest the lung will re-expand, then we think we will be able to offer Talc Pleurodesis with a greater chance of success.**

How would you feel about having an additional procedure to remove some fluid and take pressure measurements before deciding which treatment might be best?
Please tick one box

Yes, I would not mind having another procedure if it provided useful information to help me make a decision ☐
No, I am already happy with my decision and would rather not have another procedure ☐
Not sure ☐

6. **If you have any comments you would like to make about your treatment or the process of deciding what treatment to have, please write these in the box below.**

Thank you for completing this survey, please return your completed survey to the research doctor or nurse

Appendix 7 DPM and TUS Trial Specific Instructions

Pre-EDIT Trial Specific Instruction**: Digital Pleural Manometry (DPM) including Ultrasound Estimation of Pleural Effusion Volume, M-mode atelectatic lung assessment and Large Volume Thoracentesis**

Version: 2.0
Author: Geoffrey Martin
Date finalised: 23/10/2017

PRE-ASPIRATION THORACIC ULTRASOUND (TUS) ASSESSMENT

1. Record start time for TUS.
2. Position patient comfortably sitting upright at 90°.
3. Set ultrasound machine to B mode (2D).
4. Identify effusion and ipsilateral hemidiaphragm with the probe in a vertical alignment.
5. Optimise image with appropriate depth and gain settings.
6. Freeze screen at a representative lateral chest wall site in the posterior axillary line and use digital calipers to measure and record (in centimetres) the lateral height (LH), posterior height (PH) and median sub-pulmonary height of the effusion (SH) in centimetres, as shown in Figure A overleaf.
7. Where LH or PH is greater than the maximum dimensions of a single ultrasound image and therefore cannot be measured digitally, the probe and disposable skin marker should be used to mark the extent of the effusion on the chest wall. A tape measure should then be used to measure LH or PH from these markings.
8. Calculate estimated pleural effusion volume (E) as follows:

   E (ml) = (LH + SH) x 70

9. Identify effusion and ipsilateral hemidiaphragm with the probe placed on the posterior chest wall.
10. Progressively move the probe superiorly until the first image of atelectatic lung is achieved.
11. Hold the probe in this position and switch to M-mode recording.
12. Ensure M-mode region of interest is focused on atelectatic lung edge.
13. Record cine loops of this assessment over at least 3 cardiac cycles during a breath hold at the end of tidal expiration.
14. Return to B mode sonography.
15. Identify a safe catheter insertion site – where possible this should be in the posterior axiliary line in the second rib space above the costophrenic angle.
16. Mark safe insertion site with disposable marker pen.
17. Record completion time for ultrasound scan, including calculation of E and TMAV.
18. M mode analysis will be performed offline – the mean atelectatic lung edge displacement over 3 consecutive cardiac cycles will be recorded.

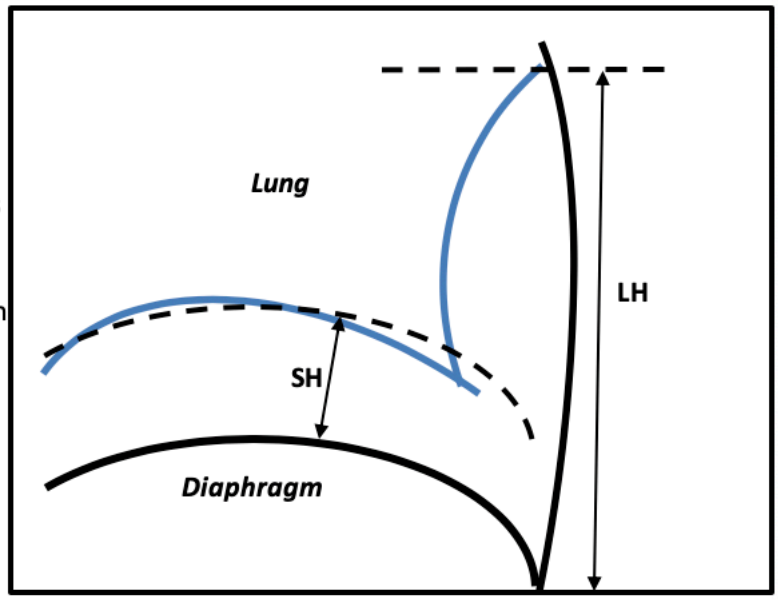


Figure A Schematic representation of the Thoracic Ultrasound measurements required to estimate pleural effusion volume (E) using the Goecke model

LH measurements should be taken in the posterior axillary line.
PH measurements should be taken immediately lateral to the tip of the spinous processes.

LARGE VOLUME THORACENTESIS WITH DPM

1. ***Preparation:***

a) Ensure no contraindication to thoracentesis (e.g. coagulopathy defined by INR >1.5 or platelet count <50)
b) Obtain informed written consent from the patient.
c) Ensure that the required equipment and assistant are available:
    a. Sterile gloves and gown
    b. Skin marker pen
    c. Antiseptic solution (chlorhexidine/alcohol or povidone iodine solution)
    d. Sterile drape and dressing pack/table cover
    e. Sterile dressing to hold catheter (eg peripheral venous cannula dressing)
    f. Rocket Medical DPM compatible pleural aspiration catheter and associated equipment:
        i. Scalpel blade
        ii. 3-way tap
        iii. 50ml leur lock syringe
        iv. 2L drainage bag
    g. 2x green (21g) and 1x orange (25g) needles
    h. 20ml syringe
    i. 1% lidocaine up to 3mg/kg, dose at discretion of operator
    j. Bio-occlusive dressing
    k. Sterile US probe cover
    l. Sterile US gel

d) Position the patient so they are sitting upright and leaning forwards against a cushioned table. Unpack equipment on to sterile field.

2. Catheter insertion:

a) Record procedure start time.
b) Wash hands and put on gown and gloves.
c) Clean the skin using anti-septic solution and create a sterile field using sterile drapes.
d) Infiltrate the skin with lidocaine using 25g needle initially to raise a bleb and then 21g needle to infiltrate intercostal muscles and costal pleura.
e) Wait 2 minutes for lidocaine to take full effect.
f) Attach transducer cable to DPM display unit and turn power on without compromising sterility of gloves/gown with help from assistant.
g) The display unit will automatically 'zero' and then display pressure (IPP)/time graph; subsequent changes in IPP the transducer experiences at the catheter sleave will now be recorded.
h) Use scalpel blade to make a 4-5mm superficial horizontal incision at marked site.
i) Insert aspiration catheter via incision aiming to pass the catheter over superior border of lower rib of marked intercostal space; indicator mark at hilt of insertion needle will change from green to red during insertion and return to green once pleural space successfully reached.
j) Once indicator green, confirm position by free aspiration of pleural fluid using 10ml syringe then advance catheter a further 1cm before twisting and disconnecting insertion needle at one-way valve.
k) Hold needle in fixed position relative to the patient and advance catheter over needle until catheter fully inserted into pleural space then withdraw needle completely.
l) Attach clamped drainage line with 3-way tap to catheter and also to drainage bag.
m) Rotate catheter to ensure that pressure transducer is level with insertion site.
n) Apply sterile dressing to hold catheter and pressure transducer in position.

3. Pleural aspiration and manometry

a) Ensure 3-way tap turned off to catheter.
b) Attach 50ml leur lock syringe to 3rd port on 3-way tap then unclamp drainage line taking care to maintain a closed system and avoid the introduction of air to the pleural space or aspiration equipment.
c) Ask assistant to document opening pleural pressure.
d) Aspirate pleural fluid in 50ml aliquots and discard into drainage bag via 3-way tap
The assistant should record end-expiratory IPP, the cumulative fluid volume removed and the time of each IPP reading at 50ml intervals. A dedicated data collection table in the CRF is provided for this purpose.
NOTE: Care should be taken to ensure an end-expiratory IPP measurement is recorded. Since the DPM equipment records a mean IPP over the preceeding 5 seconds, the patient should be coached to perform a 5 second breath hold at the end of a tidal breath at each 50ml interval.
e) At the point in time when 200, 500 and 1000ml have been aspirated, the patient will be coached to perform maximal inspiratory and expiratory manoeuvres. The patient should perform a 5 second breath hold at full inspiration and also at full expiration. The

IPP associated with each breath hold should be recorded in addition to the end-expiratory IPP.

f) At operator selected intervals, the ultrasound probe, within a sterile cover, should be placed on the patient's chest wall at a site adjacent to the aspiration catheter which would be suitable for subsequent ICD or IPC insertion and a horizontal measurement of the distance between costal pleura and atelectatic lung edge should be made.
g) Continue sequential aspiration until one of the following criteria is met;
    i. Horizontal distance between costal pleura and lung edge ≤ 30mm
    ii. Patient develops chest discomfort
    iii. Patient develops excessive coughing which they find uncomfortable
    iv. Pleural pressure ≤ -20cmH_2O
h) Record reason for termination and document closing pleural pressure.
i) With the patient holding their breath at maximal inspiration, remove the aspiration catheter and apply bio-occlusive dressing to wound.
j) Weigh filled drainage bag and subtract weight of unfilled drainage bag to obtain accurate pleural fluid volume (ΔV_{OUT}).
k) Record completion time for procedure. Calculate and record total time taken for the procedure.
l) Calculations mean pleural elastance (P_{EL}) and rolling average of P_{EL} (P_{EL250}) should then be completed whilst the patient undergoes post-procedure MRI scanning.

POST-ASPIRATION TUS ASSESSMENT

1. Position patient comfortably sitting upright at 90°
2. Set ultrasound machine to B mode (2D).
3. Identify effusion and optimize image with appropriate depth and gain settings.
4. Repeat measurement of LH and SH as described in the pre-aspiration TUS assessment.
5. Identify potential lateral insertion site for chest drain (ICD); ideally in mid- or posterior-axillary line 2 rib spaces above the costophrenic angle.
6. Freeze image in this position and use digital calipers to measure depth of fluid between costal pleura and lung edge ($D_{90°}$).
7. The patient should then be positioned in a lateral decubitus position and TUS should be performed along the mid-axillary line.
8. The diaphragm should be identified and the probe then moved superiorly until a potentially suitable indwelling pleural catheter (IPC) insertion site is identified; ideally in 2 rib spaces above the costophrenic angle in the mid- to anterior-axillary line.
9. Freeze image in this position and use digital calipers to measure depth of fluid between costal pleura and lung edge (D_{LAT}).

A standard Seldinger technique should be used for:

- ICD insertion where $D_{90°}$ is > 20mm
- IPC insertion where D_{LAT} is > 20mm

Where the minimum depth requirement is not met, a Boutin needle should be used for pleural cavity access. Details are given in Appendix 6.

Appendix 8 Pre-EDIT ICD Trial Specific Instructions

Pre-EDIT Trial Specific Instruction (TSI)**: Intercostal Chest Drain (ICD) Insertion**

Version: 1.0
Author: Geoffrey Martin
Date finalised: 16/03/2017

Introduction

This TSI describes the method which should be used for ICD insertion using a Seldinger technique for patients within the Pre-EDIT study. This will include:

- Patients receiving Standard Care
- Patients receiving EDIT Management where MaxP_{EL250} < 14.5 cm H_2O/L **AND** post-DPM TUS demonstrates sufficient residual pleural fluid for safe insertion (see Appendix 4)

Where there is insufficient residual fluid for safe insertion using a Seldinger technique, the TSI in Appendix 6 should be followed.

1. Preparation:

a) Ensure no contraindication to chest drain insertion (e.g. coagulopathy defined by INR >1.5 or platelet count <50)
b) Obtain informed written consent from the patient.
c) Ensure that the required equipment and assistant are available:
    a. Sterile gloves
    b. Skin marker pen
    c. Antiseptic solution (chlorhexidine/alcohol or povidone iodine solution)
    d. Chest drain dressing
    e. 1-0 (or thicker) silk suture
    f. Rocket Medical 12Fr Seldinger technique chest drain insertion kit
    g. 1% lidocaine up to 3mg/kg, dose at discretion of operator
    h. Chest drain bottle
    i. Chest drain tubing
    j. Sterile water for chest drain bottle
d) Position the patient so they are sitting upright and leaning forwards against a cushioned table.
e) Use thoracic ultrasound to assess the effusion and identify safe chest drain insertion site on lateral chest wall and mark with skin marker pen.
f) Wash hands.
g) Unpack equipment on to sterile field.
h) Unpack chest drain bottle and add sterile water to 'fill line'.
i) Attach chest drain tubing to drain bottle whilst maintaining the sterility of the tubing and 'fir cone' tip.

2. Chest drain insertion:

a) Wash hands and put on gown and gloves.
b) Clean the skin using anti-septic solution and create a sterile field using sterile drapes.
c) Infiltrate the skin with lidocaine using 25g needle initially to raise a bleb and then 21g needle to infiltrate intercostal muscles and costal pleura.
d) Wait 2 minutes for lidocaine to take full effect.
e) Attach 10ml syringe to introducer needle and cautiously advance this within the marked rib space at an angle perpendicular to the chest wall until pleural fluid can be freely aspirated.
f) Remove the 10ml syringe from the introducer needle and pass approximately half the length of the guide wire into the pleural cavity via the lumen of the introducer needle.
g) Remove the introducer needle over the guide wire whilst taking care to keep the guide wire in position within the pleural cavity.
h) Use the scalpel blade to make a 4mm superficial horizontal incision at the site of guide wire entry on the chest wall.
i) Thread the dilator onto the guide wire and use a firm, controlled pushing and twisting motion to advance this into the pleural cavity. The dilator safety guard should only be removed if essential for access to the costal pleura.
j) Whilst advancing the dilator, ensure it follows the same tract as the guide wire and that the wire does not become kinked or twisted.
k) Remove the dilator and hold sterile swab over wound.
l) Thread chest drain onto guide wire and advance drain the required distance into pleural cavity; this will depend upon the size of the patient's hemithorax and chest wall thickness.
m) Remove guide wire and central stiffening 'core' from chest drain whilst leaving the drain in position.
n) Attach closed 3-way tap to distal end of chest drain.
o) Suture drain in position.
p) Attach chest drain tubing to chest drain via 3-way tap and 'fir cone' connector.
q) Apply drain site dressing then remove drapes.
r) Apply tape to chest drain and 3-way tap connections.
s) Apply 40-50cm length of tape to form an 'omentum' between chest wall and the drain.

3. Post-insertion ICD management

a) Allow up to 1000ml to drain within the first hour following insertion then occlude drain output using 3-way tap for at least 1 hour before further drainage. Drainage should also be stopped if the patient develops chest discomfort during drainage.
b) A chest radiograph should be performed to assess the drain position.
c) Thereafter, aim to drain up to 500ml / hour and minimise the time spent with the drain occluded.
c) Drain output should be documented on a chest drain chart at least 4 times per day.
d) The drain should be flushed twice daily with 20ml of sterile 0.9% saline following local protocols.

Appendix 9 Pre-EDIT IPC Trial Specific Instruction

Pre-EDIT Trial Specific Instruction (TSI)**: Insertion and drainage of Indwelling Pleural Catheter (IPC)**

Version: 1.0
Author: Geoffrey Martin
Date finalised: 19/03/2017

Introduction

This TSI describes the method which should be used for IPC insertion using a Seldinger technique for patients within the Pre-EDIT study. These patients will be receiving EDIT management where $MaxP_{EL250} \geq 14.5$ cm H_2O/L **AND** post-DPM TUS demonstrates sufficient residual pleural fluid for safe insertion (see Appendix 4)

Where there is insufficient residual fluid for safe insertion using a Seldinger technique, the TSI in Appendix 6 should be followed.

1. ***Preparation:***

a) Ensure no contraindication to IPC insertion (e.g. coagulopathy defined by INR >1.5 or platelet count <50)
b) Obtain informed written consent from the patient.
c) Operator should change into 'theatre blues'.
d) Ensure that the required equipment and assistant are available:
    a. Sterile gloves and gown
    b. Skin marker pen
    c. Sterile foil bowel
    d. Bottle of sterile 0.9% saline
    e. Antiseptic solution (chlorhexidine/alcohol or povidone iodine solution)
    f. 2x 2-0 silk sutures
    g. Rocket Medical IPC insertion kit
    h. 1% lidocaine with 1:200,000 adrenaline, up to 6mg/kg, dose at discretion of operator
    i. 20ml leur lock syringe
    j. Additional 21g needle
    k. Rocket Medical IPC drainage bottle pack

e) Consider pre-medication, eg Oramorph 20mg.
f) Position the patient so they are lying in a comfortable lateral decubitus position with their head and arms adequately supported.
g) Use thoracic ultrasound to assess the effusion and identify safe IPC pleural cavity access site on lateral chest wall ('entry site') and mark with skin marker pen.
h) Use tape measure to plan IPC exit site which should be 5cm anterior and inferior of the entry site and within the same intercostal space. Mark exit site and planned subcutaneous path of IPC.
i) Wash hands.
j) Unpack equipment on to sterile field.
k) Pour 0.9% saline into foil bowel without compromising sterility.

2. IPC insertion:

a) Wash hands and put on gown and gloves.
b) Clean the skin using anti-septic solution and create a large sterile field using drapes.
c) Draw up lidocaine with adrenaline into two 20ml syringes.
d) Infiltrate the skin with lidocaine using 25g needle initially to raise a bleb at the IPC entry site and then 21g needle to infiltrate intercostal muscles and costal pleura.
e) Using the other lidocaine-filled syringe, infiltrate the skin and subcutaneous tissues from the entry site, along the intended IPC tunneling site, to the exit site.
f) Wait 2 minutes for lidocaine to take full effect.
g) Attach 10ml syringe to introducer needle and cautiously advance this at the entry site at an angle perpendicular to the chest wall until pleural fluid can be freely aspirated.
h) Remove the 10ml syringe from the introducer needle and pass approximately half the length of the guide wire into the pleural cavity via the lumen of the introducer needle.
i) Remove the introducer needle over the guide wire whilst taking care to keep the guide wire in position within the pleural cavity. Anchor the distal tip of the guide wire using the weight of damp sterile swabs.
j) Use the scalpel blade to make an approximately 7mm superficial horizontal incision at the site of guide wire entry on the chest wall and also at the planned IPC exit site.
k) Use the forceps and blunt dissection to create a subcutaneous IPC tunnel between the entry and exit sites.
l) Moisten the drainage catheter using sterile saline.
m) Using the plastic trocar, place the drainage catheter in the subcutaneous tunnel such that the distal end of the catheter is closest to the exit site and the Dacron cuff is approximately 1 cm from the entry site.
n) Remove the plastic trocar from the drain tip and clean drain with a moistened swab.
o) Thread the dilator onto the guide wire and use a firm, controlled pushing and twisting motion to advance this into the pleural cavity.
p) Whilst advancing the dilator, ensure it follows the same tract as the guide wire and that the wire does not become kinked or twisted.
q) Remove the dilator leaving the dark grey cuff in situ.
r) Pass the drainage catheter into the pleural space via the dark grey cuff which should be split and removed to allow complete subcutaneous passage of the catheter.
s) Check position of Dacron cuff – this should now be approximately 1cm from exit site. If required, the catheter may be pulled back to optimise its position.
t) Close entry site wound with 2 sutures.
u) Close exit site wound and secure IPC with a further 2 sutures.
v) Clean and dry wounds and surrounding skin.
w) Attach IPC drainage bottle and drain up to 600ml if the patient is comfortable during drainage.
x) Remove drainage bottle and apply cap to IPC valve.
y) Apply IPC dressing, ensuring both wounds are covered and the IPC is neatly coiled between the top dressing and the foam pad.

3. Post-insertion IPC management

a) A chest radiograph should be performed to assess and document the IPC position.
b) Patient should be admitted to ward 7B.
c) A further drainage of up to 600ml should take place on the evening of insertion. This will be performed by suitably trained staff on the ward. Drainage will be stopped at the onset of any chest pain, 'tugging' or discomfort.
d) The following morning a further drainage of up to 600ml should be attempted.
e) Following discharge, domiciliary IPC drainage will take place by suitably trained district nursing staff. All patients will initially undergo daily drainage.
f) Drainage frequency will be reduced sequentially each time < 400ml is aspirated on 2 consecutive occasions following the intervals below:

- Initially daily
- Three times per week
- Twice per week
- Once weekly
- Once fortnightly

g) Where < 400ml is regularly aspirated fortnightly, consideration will be given to IPC removal which will be at the discretion of the primary physician.

Appendix 10 Proposed EDIT trial synopsis

Title	**EDIT:** A randomised Phase III trial testing the effect of **E**lastance-**D**irected **I**ntra-pleural catheter or **T**alc Pleurodesis (EDIT) management on pleurodesis failure rate in Malignant Pleural Effusion	
Design	Multi-centre, randomised (1:1), open-label superiority trial	
Trial Participants	Patients with symptomatic Malignant Pleural Effusion without clinically obvious non-expansile lung (NEL)	
Sample Size	In order to detect a reduction in TP failure rate from 25% in the control arm (talc pleurodesis) to 10% in the intervention arm (EDIT), with 90% power, a 2-sided α = 0.05, and assuming a 10% loss to follow-up, 292 patients are required (146 patients in each arm).	
Trial Centres	Lead Centre: Glasgow Participating Centres: 10 UK (+/- US) Pleural Disease Centres	
Trial Coordination	Cancer Research-UK Glasgow Clinical Trials Unit	
Trial Period	36 months [Set up: 6 months, Recruitment: 24 months, Follow-up: 6 months]	
Sponsor	NHS Greater Glasgow & Clyde	
Funding	Charitable grant from Clydeside Action on Asbestos and an unrestricted commercial grant from Rocket Medical (UK)	
	Trial Objectives	**Associated End-points**
Primary	To determine whether EDIT management reduces TP failure rate from 25% in the control arm to 10% in the intervention arm	TP failure, as defined by the need for repeat ipsilateral pleural intervention for recurrent symptomatic pleural effusion, within 3 months of randomisation.
Secondary	To determine the diagnostic performance of the P_{EL} threshold used to allocate patients in the EDIT arm to placement of an IPC	Sensitivity and Specificity (of $MaxP_{EL250} \geq 14.5$ cm H_2O/L) relative to radiologically defined NEL
	To determine the safety and tolerability of EDIT management	Adverse Events (AE) and Serious AE (SAE) rate. The occurrence of chest pain, cough or breathlessness.

	To determine the health economic impact of EDIT management	Total healthcare costs, including those associated with index treatment and all subsequent attendances, including re-admissions
	To determine the diagnostic utility of M-mode assessment of cardiac impulse lung displacement for NEL	M-mode assessment of cardiac impulse lung displacement relative to radiologically defined NEL

Eligibility Criteria	**Inclusion Criteria:**
	• Clinically confident diagnosis of MPE, defined as any of the following:
	  o Pleural effusion with histo-cytologically proven pleural malignancy **OR**
	  o Pleural effusion in the context of histo-cytologically proven malignancy elsewhere, without a clear alternative cause for fluid **OR**
	  o Pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging (CT/MRI)
	• Degree of breathlessness for which therapeutic pleural intervention would be offered
	• Age >18 years
	• Expected survival > 3 months
	• Written Informed Consent	

	Exclusion Criteria: • Clinical suspicion of NEL or known expansion status • Patient preference for 1st-line IPC insertion • Previous ipsilateral failed TP • Any C/I to chest drain or IPC insertion, including irreversible coagulopathy, inaccessible pleural collection or lack of suitable IPC tunnel site • Females who are pregnant or lactating	

Screening and Consent	Patients with symptomatic MPE will be identified at cancer MDTs, routine outpatient appointments, and during inpatient reviews. Those patients meeting all Inclusion Criteria and without assessable Exclusion Criteria will be provided with a Patient Information Sheet (PIS) and given sufficient time to consider participation. There must be at least 24 hours between the patient receiving the PIS and giving consent to trial participation. Consent will be a two-stage process. After initial introduction to the trial, a member of clinical staff, usually a nurse specialist will make separate contact with the patient to assess whether they wish to consider participation. This will typically be done the following day. If patients are agreeable to trial involvement, a member of the research team, usually a research fellow or nurse will identify a suitable opportunity to address any questions and to seek written informed consent to screening. Formal screening will allow complete assessment for potential exclusion criteria. Patients meeting all eligibility criteria then give additional written consent to randomisation and trial enrolment.	
Randomisation and Allocation	Following consent and baseline assessments, patients will be randomised using an online system (sealedenvelope.com) and allocated 1:1 using random permuted blocks to one of two groups: • **Intervention arm: EDIT management** • **Control arm: Talc Slurry Pleurodesis**	
Recruitment Rate	The lead centre will recruit at least 30 patients/year over the study period. Up to 10 additional centres within the UK (+/- US) will recruit 10-20 patients per year.	
Trial Procedures	**Intervention: EDIT management** 1. Large volume pleural aspiration with recording of IPP and V_{OUT} after every 50ml of fluid aspirated 2. Computation of Peak P_{EL250}, defined as the rolling average P_{EL} over preceding 250ml aspirated. **MaxP_{EL250} ≥ 14.5 cm H_2O/L at any point**: allocated to IPC **MaxP_{EL250} < 14.5 cm H_2O/L at all points**: allocated to TP 3. EDIT-directed 1st-line treatment, using the manometry catheter to place a guidewire, facilitating immediate ICD or IPC placement based on **MaxP_{EL250}**	**Control: TSP** TSP performed according to BTS guidelines

<table>
<tr><td></td><td></td></tr>
<tr><td></td><td>Re-intervention criteria in both arms:
The need for repeat pleural intervention for symptomatic recurrence of effusion will be based on the treating clinician’s judgment, assuming at least 50% of the ipsilateral hemithorax is occupied by fluid on the PA chest radiograph. If <50% fluid recollection, the agreement of a blinded colleague must be sought before intervention.

Trial Follow-up Visits
Patients in both treatment arms will receive identical follow-up, including trial visits, ideally combined with routine clinical appointments at 4 weeks and 3 months after treatment. Electronic review of case records +/- telephone visit will be permitted in patients unfit to attend clinic.</td></tr>
<tr><td>End of Trial</td><td>The trial will end after all 292 patients have been recruited and all have completed their 3-month follow up appointment, or have died whichever occurs first.</td></tr>
<tr><td>Procedures for Safe Monitoring</td><td>All AEs will be reported directly to the sponsor. Any unexpected SAEs that are related to the use of the DPM or subsequent pleural procedures in the EDIT management arm will be subject to expedited reporting.</td></tr>
<tr><td>Trial Costs</td><td>Detailed trial costs will be generated after a decision on the feasibility of commercial support via Rocket Medical (UK). The outline costs provided below are likely to be broadly representative and are based on recently funded clinical trials in the lead centre. These costs assume that EDIT management consumables (Rocket DPM) will be supplied by Rocket Medical UK.

<table>
<tr><th></th><th>Year 1</th><th>Year 2</th><th>Year 3</th><th>Category Total</th></tr>
<tr><td>CRUK-CTU costs</td><td></td><td></td><td></td><td></td></tr>
<tr><td>1. Project Manager</td><td>10,678</td><td>10,678</td><td>10,678</td><td>32,034</td></tr>
<tr><td>2. Trial Statistician</td><td>10,488</td><td>10,488</td><td>10,488</td><td>31,464</td></tr>
<tr><td>3. IT programmer</td><td>3,949</td><td>3,949</td><td>3,949</td><td>11,847</td></tr>
<tr><td>4. Clinical Trial Coordinator</td><td>6,594</td><td>6,594</td><td>6,594</td><td>19,782</td></tr>
<tr><td>5. Trial Registration,Office Costs</td><td>8,250</td><td>0</td><td>0</td><td>8,250</td></tr>
<tr><td>Clinical Research Fellow</td><td>62,600</td><td>62,600</td><td>62,600</td><td>187,800</td></tr>
<tr><td>Trial Visits</td><td>5,000</td><td>10,000</td><td>5,000</td><td>20,000</td></tr>
<tr><td>EDIT Consumables</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>Site training & Initiation Visits</td><td>5,000</td><td>0</td><td>0</td><td>5,000</td></tr>
<tr><td>Total</td><td>112,559</td><td>104,309</td><td>99,309</td><td>316,177</td></tr>
</table>
</td></tr>
</table>

References

1. Clive AO, Kahan BC, Hooper CE, Bhatnagar R, Morley AJ, Zahan-Evans N, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax. BMJ Publishing Group Ltd; 2014 Dec;69(12):1098–104.

2. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, 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. American Medical Association; 2012 Jun 13;307(22):2383–9.

3. Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, 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. American Medical Association; 2017 Nov 21;318(19):1903–12.

4. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ, BTS Pleural Disease Guideline Group. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. Vol. 65 Suppl 2, Thorax. BMJ Publishing Group Ltd and British Thoracic Society; 2010. pp. ii32–40.

5. Dresler CM, Olak J, Herndon JE, Richards WG, Scalzetti E, Fleishman SB, et al. Phase III intergroup study of talc poudrage vs talc slurry sclerosis for malignant pleural effusion. Chest. 2005 Mar;127(3):909–15.

6. Marel M, Zrůstová M, Stasný B, Light RW. The incidence of pleural effusion in a well-defined region. Epidemiologic study in central Bohemia. Chest. 1993 Nov;104(5):1486–9.

7. Rahman NM, Ali NJ, Brown G, Chapman SJ, Davies RJO, Downer NJ, et al. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. Vol. 65 Suppl 2, Thorax. BMJ Publishing Group Ltd and British Thoracic Society; 2010. pp. ii54–60.

8. Chernow B, Sahn SA. Carcinomatous involvement of the pleura: an analysis of 96 patients. Am J Med. 1977 Nov;63(5):695–702.

9. Psallidas I, Yousuf A, Talwar A, Hallifax RJ, Mishra EK, Corcoran JP, et al. Assessment of patient-reported outcome measures in pleural interventions. BMJ Open Respir Res. Archives of Disease in childhood; 2017;4(1):e000171.

10. Taghizadeh N, Fortin M, Tremblay A. US Hospitalizations for Malignant Pleural Effusions: Data From the 2012 National Inpatient Sample. Chest. 2017 Apr;151(4):845–54.

11. Rahman N, Wang N-S. Anatomy of the pleura. In: Textbook of Pleural Diseases Second Edition. CRC Press; 2012. pp. 13–25.

12. West JB, Fu Z, Gaeth AP, Short RV. Fetal lung development in the elephant reflects the adaptations required for snorkeling in adult life. Respiratory Physiology & Neurobiology. Elsevier; 2003 Nov 14;138(2-3):325–33.

13. NOPPEN M, DE WAELE M, LI R, GUCHT KV, D'HAESE J, GERLO E, et al. Volume and Cellular Content of Normal Pleural Fluid in Humans Examined by Pleural Lavage. Am J Respir Crit Care Med. 2000 Sep;162(3):1023–6.

14. Miserocchi G. Physiology and pathophysiology of pleural fluid turnover. Eur Respir J. 1997 Jan;10(1):219–25.

15. Rodrîguez-Panadero F, Borderas Naranjo F, López Mejîas J. Pleural metastatic tumours and effusions. Frequency and pathogenic mechanisms in a post-mortem series. Eur Respir J. 1989 Apr;2(4):366–9.

16. Light RW, Hamm H. Malignant pleural effusion: would the real cause please stand up? Eur Respir J. 1997 Aug;10(8):1701–2.

17. Meyer PC. Metastatic carcinoma of the pleura. Thorax. BMJ Publishing Group; 1966 Sep;21(5):437–43.

18. Thomas R, Jenkins S, Eastwood PR, Lee YCG, Singh B. Physiology of breathlessness associated with pleural effusions. Curr Opin Pulm Med. 2015 Jul;21(4):338–45.

19. Burki NK, Lee L-Y. Mechanisms of dyspnea. Chest. 2010 Nov;138(5):1196–201.

20. Clive AO, Kahan BC, Hooper CE, Bhatnagar R, Morley AJ, Zahan-Evans N, et al. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. Thorax. 2014 Nov 11;69(12):1098–104.

21. Psallidas I, Kanellakis NI, Gerry S, Thézénas ML, Charles PD, Samsonova A, et al. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. Lancet Oncol. 2018 Jul;19(7):930–9.

22. American Thoracic Society. Management of malignant pleural effusions. Vol. 162, American journal of respiratory and critical care medicine. American Thoracic SocietyNew York, NY; 2000. pp. 1987–2001.

23. Livingston RB, McCracken JD, Trauth CJ, Chen T. Isolated pleural effusion in small cell lung carcinoma: favorable prognosis. A review of the Southwest Oncology Group experience. Chest. 1982 Feb;81(2):208–11.

24. Clive AO, Bhatnagar R, Preston NJ, Maskell NA, Jones HE. Cochrane corner: interventions for the management of malignant pleural effusions. Thorax. BMJ Publishing Group Ltd and British Thoracic Society; 2016 Jul 14;:thoraxjnl–2016–208989.

25. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. Shaw PH, editor. Cochrane Database Syst Rev. Chichester, UK: John Wiley & Sons, Ltd; 2004;31A(1):CD002916.

26. Bhatnagar R, Piotrowska HEG, Laskawiec-Szkonter M, Kahan BC, Luengo-Fernandez R, Pepperell JCT, et al. Effect of Thoracoscopic Talc Poudrage vs Talc Slurry via Chest Tube on Pleurodesis Failure Rate Among Patients With Malignant Pleural Effusions: A Randomized Clinical Trial. JAMA. American Medical Association; 2019 Dec 5;323(1):60–9.

27. Rahman NM, Pepperell J, Rehal S, Saba T, Tang A, Ali N, et al. Effect of Opioids vs NSAIDs and Larger vs Smaller Chest Tube Size on Pain Control and Pleurodesis Efficacy Among Patients With Malignant Pleural Effusion: The TIME1 Randomized Clinical Trial. JAMA. 2015 Dec;314(24):2641–53.

28. Rintoul RC, Ritchie AJ, Edwards JG, Waller DA, Coonar AS, Bennett M, et al. Efficacy and cost of video-assisted thoracoscopic partial pleurectomy versus talc pleurodesis in patients with malignant pleural mesothelioma (MesoVATS): an open-label, randomised, controlled trial. Lancet. 2014 Sep 20;384(9948):1118–27.

29. Matthews C, Freeman C, Sharples LD, Fox-Rushby J, Tod A, Maskell NA, et al. MesoTRAP: a feasibility study that includes a pilot clinical trial comparing video-assisted thoracoscopic partial pleurectomy decortication with indwelling pleural catheter in patients with trapped lung due to malignant pleural mesothelioma designed to address recruitment and randomisation uncertainties and sample size requirements for a phase III trial. BMJ Open Respir Res. Archives of Disease in childhood; 2019;6(1):e000368.

30. Bhatnagar R, Corcoran JP, Maldonado F, Feller-Kopman D, Janssen J, Astoul P, et al. Advanced medical interventions in pleural disease. Eur Respir Rev. European Respiratory Society; 2016 Jun;25(140):199–213.

31. Bhatnagar R, Maskell NA. Indwelling pleural catheters. Respiration. Karger Publishers; 2014;88(1):74–85.

32. Tremblay A, Michaud G. Single-Center Experience With 250 Tunnelled Pleural Catheter Insertions for Malignant Pleural Effusion. Chest. Elsevier; 2006 Feb 1;129(2):362–8.

33. Azzopardi M, Thomas R, Muruganandan S, Lam DCL, Garske LA, Kwan BCH, et al. Protocol of the Australasian Malignant Pleural Effusion-2 (AMPLE-2) trial: a multicentre randomised study of aggressive versus symptom-guided drainage via indwelling pleural catheters. BMJ Open. 2016 Jul 5;6(7):e011480.

34. Wahidi MM, Reddy C, Yarmus L, Feller-Kopman D, Musani A, Shepherd RW, et al. Randomized Trial of Pleural Fluid Drainage Frequency in Patients with Malignant Pleural Effusions. The ASAP Trial. Am J Respir Crit Care Med. American Thoracic Society; 2017 Apr 15;195(8):1050–7.

35. Muruganandan S, Azzopardi M, Fitzgerald DB, Shrestha R, Kwan BCH, Lam DCL, et al. Aggressive versus symptom-guided drainage of malignant pleural effusion via indwelling pleural catheters (AMPLE-2): an open-label randomised trial. Lancet Respir Med. 2018 Jul 20.

36. Putnam JB, Light RW, Rodriguez RM, Ponn R, Olak J, Pollak JS, et al. A randomized comparison of indwelling pleural catheter and doxycycline pleurodesis in the management of malignant pleural effusions. Cancer. 1999 Nov 15;86(10):1992–9.

37. Demmy TL, Gu L, Burkhalter JE, Toloza EM, D'Amico TA, Sutherland S, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). J Natl Compr Canc Netw. 2012 Aug;10(8):975–82.

38. Boshuizen RC, vander Noort V, Burgers JA, Herder GJM, Hashemi SMS, Hiltermann TJN, et al. A randomized controlled trial comparing indwelling pleural catheters with talc pleurodesis (NVALT-14). Lung Cancer. 2017 Jun;108:9–14.

39. Iyer NP, Reddy CB, Wahidi MM, Lewis SZ, Diekemper RL, Feller-Kopman D, et al. Indwelling Pleural Catheter versus Pleurodesis for Malignant Pleural Effusions. A Systematic Review and Meta-Analysis. Ann Am Thorac Soc. American Thoracic Society; 2019 Jan;16(1):124–31.

40. Olfert JAP, Penz ED, Manns BJ, Mishra EK, Davies HE, Miller RF, et al. Cost-effectiveness of indwelling pleural catheter compared with talc in malignant pleural effusion. Respirology. 2017 May;22(4):764–70.

41. Penz ED, Mishra EK, Davies HE, Manns BJ, Miller RF, Rahman NM. Comparing cost of indwelling pleural catheter vs talc pleurodesis for malignant pleural effusion. Chest. 2014 Oct;146(4):991–1000.

42. Fysh ETH, Tremblay A, Feller-Kopman D, Mishra EK, Slade M, Garske L, et al. Clinical outcomes of indwelling pleural catheter-related pleural infections: an international multicenter study. Chest. 2013 Nov;144(5):1597–602.

43. Seymour J, Psallidas I, Dobson M, Rahman N. The patient perspective of treatment for Malignant Pleural Effusion (MPE)- results of a pilot service-evaluation questionnaire. European Respiratory Journal. European Respiratory Society; 2018 Sep 15;52(suppl 62):PA2882.

44. Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. N Engl J Med. 2018 Apr 5;378(14):1313–22.

45. Bhatnagar R, Zahan-Evans N, Kearney C. The SEAL-MPE Trial: A phase I safety evaluation of a novel silver nitrate coated indwelling pleural catheter. B36 PLEURAL …. 2016.

46. Feller-Kopman DJ, Reddy CB, DeCamp MM, Diekemper RL, Gould MK, Henry T, et al. Management of Malignant Pleural Effusions. An Official ATS/STS/STR Clinical Practice Guideline. Am J Respir Crit Care Med. 2018 Oct 1;198(7):839–49.

47. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur J Cardiothorac Surg. 2018 Jul 27.

48. Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. N Engl J Med. 2018 Apr 5;378(14):1313–22.

49. Doelken P. Clinical implications of unexpandable lung due to pleural disease. Am J Med Sci. 2008 Jan;335(1):21–5.

50. Huggins JT, Doelken P, Sahn SA. The unexpandable lung. F1000 Med Rep. 2010;2(77):77.

51. Huggins JT, Maldonado F, Chopra A, Rahman N, Light R. Unexpandable lung from pleural disease. Respirology. John Wiley & Sons, Ltd; 2018 Feb;23(2):160–7.

52. Raptopoulos V, Davis LM, Lee G, Umali C, Lew R, Irwin RS. Factors affecting the development of pneumothorax associated with thoracentesis. AJR Am J Roentgenol. American Public Health Association; 1991 May;156(5):917–20.

53. Duncan DR, Morgenthaler TI, Ryu JH, Daniels CE. Reducing iatrogenic risk in thoracentesis: establishing best practice via experiential training in a zero-risk environment. Chest. 2009 May;135(5):1315–20.

54. Ault MJ, Rosen BT, Scher J, Feinglass J, Barsuk JH. Thoracentesis outcomes: a 12-year experience. Thorax. BMJ Publishing Group Ltd and British Thoracic Society; 2015 Feb;70(2):127–32.

55. Heidecker J, Huggins JT, Sahn SA, Doelken P. Pathophysiology of pneumothorax following ultrasound-guided thoracentesis. Chest. 2006 Oct;130(4):1173–84.

56. Corcoran JP, Tazi-Mezalek R, Maldonado F, Yarmus LB, Annema JT, Koegelenberg CFN, et al. State of the art thoracic ultrasound: intervention and therapeutics. Thorax. BMJ Publishing Group Ltd; 2017 Sep 1;72(9):840–9.

57. Corcoran JP, Hallifax RJ, Mercer RM, Yousuf A, Asciak R, Hassan M, et al. Thoracic Ultrasound as an Early Predictor of Pleurodesis Success in Malignant Pleural Effusion. Chest. 2018 Nov;154(5):1115–20.

58. Psallidas I, Piotrowska HEG, Yousuf A, Kanellakis NI, Kagithala G, Mohammed S, et al. Efficacy of sonographic and biological pleurodesis indicators of malignant pleural effusion (SIMPLE): protocol of a randomised controlled trial. BMJ Open Respir Res. 2017;4(1):e000225.

59. Sivakumar P, Douiri A, West A, Rao D, Warwick G, Chen T, 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 Oct 18;6(10):e012795.

60. Chopra A, Judson MA, Doelken P, Maldonado F, Rahman NM, Huggins JT. The Relationship of Pleural Manometry With Postthoracentesis Chest

Radiographic Findings in Malignant Pleural Effusion. Chest. 2019 Aug 28;157(2):421–6.

61. Huggins JT, Sahn SA, Heidecker J, Ravenel JG, Doelken P. Characteristics of trapped lung: pleural fluid analysis, manometry, and air-contrast chest CT. Chest. 2007 Jan;131(1):206–13.

62. Qureshi RA, Collinson SL, Powell RJ, Froeschle PO, Berrisford RG. Management of malignant pleural effusion associated with trapped lung syndrome. Asian Cardiovasc Thorac Ann. 2008 Apr;16(2):120–3.

63. Ip H, Ahmed S, Noorzad F, West A, Ahmed L. M24 Non-expandable lung in malignant pleural effusions at medical thoracoscopy. Thorax. BMJ Publishing Group Ltd; 2018 Dec 1;73(Suppl 4):A259–9.

64. Hallifax RJ, Corcoran JP, Psallidas I, Rahman NM. Medical thoracoscopy: Survey of current practice-How successful are medical thoracoscopists at predicting malignancy? Respirology. 2016 Jul;21(5):958–60.

65. Salamonsen M, Ware R, Fielding D. A new method for performing continuous manometry during pleural effusion drainage. Respiration. Karger Publishers; 2014;88(1):61–6.

66. Light RW, Jenkinson SG, Minh VD, George RB. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. Am Rev Respir Dis. 1980 May;121(5):799–804.

67. Lan RS, Lo SK, Chuang ML, Yang CT, Tsao TC, Lee CH. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. Ann Intern Med. 1997 May 15;126(10):768–74.

68. Feller-Kopman D, Ernst A. Pleural manometry. In: Textbook of Pleural Diseases Second Edition. 3rd ed. CRC Press; 2012. pp. 227–32.

69. Huggins JT, Doelken P. Pleural manometry. Clin Chest Med. 2006 Jun;27(2):229–40.

70. Lee HJ, Yarmus L, Kidd D, Ortiz R, Akulian J, Gilbert C, et al. Comparison of pleural pressure measuring instruments. Chest. 2014 Oct;146(4):1007–12.

71. Doelken P, Huggins JT, Pastis NJ, Sahn SA. Pleural manometry: technique and clinical implications. Chest. 2004 Dec;126(6):1764–9.

72. Feller-Kopman D, Parker MJ, Schwartzstein RM. Assessment of pleural pressure in the evaluation of pleural effusions. Chest. 2009 Jan;135(1):201–9.

73. Havelock T, Teoh R, Laws D, Gleeson F, BTS Pleural Disease Guideline Group. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. Vol. 65 Suppl 2, Thorax. BMJ Publishing Group Ltd and British Thoracic Society; 2010. pp. ii61–76.

74. Pavlin J, Cheney FW. Unilateral pulmonary edema in rabbits after reexpansion of collapsed lung. J Appl Physiol Respir Environ Exerc Physiol. 1979 Jan;46(1):31–5.

75. Feller-Kopman D, Berkowitz D, Boiselle P, Ernst A. Large-volume thoracentesis and the risk of reexpansion pulmonary edema. Ann Thorac Surg. Elsevier; 2007 Nov;84(5):1656–61.

76. Lentz RJ, Lerner AD, Pannu JK, Merrick CM, Roller L, Walston C, et al. Routine monitoring with pleural manometry during therapeutic large-volume thoracentesis to prevent pleural-pressure-related complications: a multicentre, single-blind randomised controlled trial. Lancet Respir Med. 2019 Feb 13.

77. Feller-Kopman D, Walkey A, Berkowitz D, Ernst A. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. Chest. 2006 Jun;129(6):1556–60.

78. Tsim S, Kelly C, Alexander L, McCormick C, Thomson F, Woodward R, et al. Diagnostic and Prognostic Biomarkers in the Rational Assessment of Mesothelioma (DIAPHRAGM) study: protocol of a prospective, multicentre, observational study. BMJ Open. 2016 Nov 24;6(11):e013324.

79. McLoud TC, Flower CD. Imaging the pleura: sonography, CT, and MR imaging. AJR Am J Roentgenol. 1991 Jun;156(6):1145–53.

80. Cranney GB, Lotan CS, Dean L, Baxley W, Bouchard A, Pohost GM. Left ventricular volume measurement using cardiac axis nuclear magnetic resonance imaging. Validation by calibrated ventricular angiography. Circulation. 1990 Jul;82(1):154–63.

81. Benjelloun H, Cranney GB, Kirk KA, Blackwell GG, Lotan CS, Pohost GM. Interstudy reproducibility of biplane cine nuclear magnetic resonance measurements of left ventricular function. Am J Cardiol. 1991 Jun 15;67(16):1413–20.

82. Childs H, Ma L, Ma M, Clarke J, Cocker M, Green J, et al. Comparison of long and short axis quantification of left ventricular volume parameters by cardiovascular magnetic resonance, with ex-vivo validation. J Cardiovasc Magn Reson. BioMed Central; 2011;13(1):40.

83. Grothues F, Smith GC, Moon JCC, Bellenger NG, Collins P, Klein HU, et al. Comparison of interstudy reproducibility of cardiovascular magnetic resonance with two-dimensional echocardiography in normal subjects and in patients with heart failure or left ventricular hypertrophy. Am J Cardiol. 2002 Jul 1;90(1):29–34.

84. Bhatnagar R, Laskawiec-Szkonter M, Piotrowska HEG, Kahan BC, Hooper CE, Davies HE, et al. Evaluating the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial): protocol of an open-label randomised controlled trial. BMJ Open. British Medical Journal Publishing Group; 2014 Nov 26;4(11):e007045.

85. Rahman NM, Maskell NA, West A, Teoh R, Arnold A, Mackinlay C, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. N Engl J Med. 2011 Aug 11;365(6):518–26.

86. Bibby AC, Halford P, De Fonseka D, Morley AJ, Smith S, Maskell NA. The Prevalence and Clinical Relevance of Non-expandable Lung in Malignant Pleural Mesothelioma: A Prospective, Single-Center Cohort Study of 229 Patients. Ann Am Thorac Soc. 2019 Jun 12;:AnnalsATS.201811–786OC.

87. Goecke W, Schwerk WB. Die diagnostishce Wertigkeit der Sonographie in der Identifikation von Pleuraergussen im Vergleich zur konventionellen Rontgen-Thoraxaufnahme. In: J G, BJ H, Klinggräff G von, K S, editors. Ultraschalldiagnostik. Berlin/Heidelberg/New York/Tokio; 1990. pp. 385–7.

88. Paddock FK. The relationship between the specific gravity and the protein content in human serous effusions. Am J Med Sci. 1941 Apr;201(4):569–74.

89. Landis JR, Koch GG. The Measurement of Observer Agreement for Categorical Data. Biometrics. 1977 Mar;33(1):159.

90. Leemans J, Dooms C, Ninane V, Yserbyt J. Success rate of medical thoracoscopy and talc pleurodesis in malignant pleurisy: A single-centre experience. Respirology. Wiley/Blackwell (10.1111); 2018;23(6):613–7.

91. Boutin C, Rey F, Gouvernet J, Viallat JR, Astoul P, Ledoray V. Thoracoscopy in pleural malignant mesothelioma: a prospective study of 188 consecutive patients. Part 2: Prognosis and staging. Cancer. 1993 Jul 15;72(2):394–404.

92. Martin GA, Tsim S, Kidd AC, Foster JE, McLoone P, Chalmers A, et al. Pre-EDIT: protocol for a randomised feasibility trial of elastance-directed intrapleural catheter or talc pleurodesis (EDIT) in malignant pleural effusion. BMJ Open Respir Res. 2018;5(1):e000293.

93. Bhatnagar R, Keenan EK, Morley AJ, Kahan BC, Stanton AE, Haris M, et al. Outpatient Talc Administration by Indwelling Pleural Catheter for Malignant Effusion. N Engl J Med. 2018 Apr 5;378(14):1313–22.

94. Salamonsen MR, Lo AKC, Ng ACT, Bashirzadeh F, Wang WYS, Fielding DIK. Novel use of pleural ultrasound can identify malignant entrapped lung prior to effusion drainage. Chest. 2014 Nov;146(5):1286–93.

95. Doelken P, Sahn SA. Trapped lung. Semin Respir Crit Care Med. Copyright © 2001 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA. Tel.: +1(212) 584-4662; 2001 Dec;22(6):631–6.

96. Walters SJ, Bonacho Dos Anjos Henriques-Cadby I, Bortolami O, Flight L, Hind D, Jacques RM, et al. Recruitment and retention of participants in randomised controlled trials: a review of trials funded and published by the United Kingdom Health Technology Assessment Programme. BMJ Open. British Medical Journal Publishing Group; 2017 Mar 20;7(3):e015276.