BMJ Open Respiratory Research

Pre-EDIT: protocol for a randomised feasibility trial of elastance-directed intrapleural catheter or talc pleurodesis (EDIT) in malignant pleural effusion

Geoffrey A Martin,[1,2] Selina Tsim,[1,2] Andrew C Kidd,[1] John E Foster,[3] Philip McLoone,[4] Anthony Chalmers,[2,5] Kevin G Blyth[1,6]

To cite: Martin GA, Tsim S, Kidd AC, *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 Resp Res* 2018;**5**:e000293. doi:10.1136/bmjresp-2018-000293

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjresp-2018-000293).

Received 6 March 2018
Revised 5 April 2018
Accepted 27 March 2018

[1]Pleural Disease Unit, Queen Elizabeth University Hospital, Glasgow, UK
[2]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK
[3]Glasgow Clinical Research Imaging Facility, Queen Elizabeth University Hospital, Glasgow, UK
[4]Institute of Health and Wellbeing, University of Glasgow, Glasgow, UK
[5]Clinical Oncology, Beatson West of Scotland Cancer Centre, Glasgow, UK
[6]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK

Correspondence to
Dr Kevin G Blyth;
kevin.blyth@glasgow.ac.uk

ABSTRACT

Introduction Non-expansile lung (NEL) is a common cause of talc pleurodesis (TP) failure in malignant pleural effusion (MPE), but is often occult prior to drainage. Reliable detection of NEL would allow patients to be allocated between intrapleural catheter (IPC) and TP. High pleural elastance (P_{EL}) has been associated with NEL in observational studies. Pre-EDIT is a randomised feasibility trial of elastance-directed IPC or TP (EDIT) management using a novel, purpose-built digital pleural manometer (Rocket Medical, UK).

Methods and analysis Consecutive patients with MPE without prior evidence of NEL or preference for IPC will be randomised 1:1 between EDIT management and standard care (an attempt at TP). The primary objective is to determine whether sufficient numbers of patients (defined as 30 within 12 months (or 15 over 6 months)) can be recruited and randomised to justify a subsequent phase III trial testing the efficacy of EDIT management. Secondary objectives include safety, technical feasibility and validation of study design elements, including the definition of P_{EL} using 4D pleural MRI before and after fluid aspiration. EDIT involves P_{EL} assessment during a large volume pleural fluid aspiration, followed by an attempt at TP or placement of an IPC within 24 hours. Patients will be allocated to IPC if the rolling average P_{EL} sustained over at least 250 mL fluid aspirated (P_{EL250}) is ≥ 14.5 cm H_2O/L.

Ethics and dissemination Pre-EDIT was approved by the West of Scotland Regional Ethics Committee on 8 March 2017 (Ref: 17/WS/0042). Results will be presented at scientific meetings and published in peer-reviewed journals.

Trial registration number NCT03319186; Pre-results.

Strengths and limitations of this study

- A prospective assessment of the feasibility of a novel, pleural elastance (P_{EL})-directed treatment pathway (EDIT management) for malignant pleural effusion.
- It utilises purpose-built digital pleural manometry equipment allowing continuous intrapleural pressure recording, and derivation of P_{EL} via a user-friendly interface.
- It includes pre-aspiration and post-aspiration 4D pleural MRI to validate assumptions regarding anatomical changes during fluid aspiration, the computation of P_{EL} and the origin of symptoms, such as cough and chest pain.
- It is a single-centre feasibility study; not powered to evaluate the efficacy of EDIT management but will inform the design a larger future trial using a patient-centred primary outcome measure.

INTRODUCTION

Malignant pleural effusion (MPE) is a common clinical condition and frequently leads to disabling breathlessness. Survival in patients with MPE is notably heterogeneous and is determined primarily by tumour type. However, most patients survive for less than a year and in some, this may be limited to a few months.[1] Efficient palliation of MPE symptoms is therefore a major priority for patients and their families. This is currently achieved either by admission to hospital for intercostal drain placement and an attempt at talc pleurodesis (TP) or outpatient placement of an indwelling pleural catheter (IPC).[2] When successful, TP results in durable symptom control after a 4–7 day hospital stay, and obviates the need for intermittent, domiciliary drainage and the risk of ongoing complications including pleural infection. However, non-expansile lung (NEL) frequently complicates an attempt at TP and cannot be reliably predicted using baseline radiology or other parameters. Since an IPC will effectively palliate most MPEs, regardless of NEL,[2] some centres advocate their use in all patients with MPE. However, an IPC is not acceptable to some patients. Anecdotally, this is particularly the case if immunosuppressive cancer therapy is planned, or their lifestyle or environment makes IPC management inconvenient or overly restrictive (eg, patients who enjoy swimming or reside in a warm climate).

Figure 1 Rocket Medical (UK) digital pleural manometer and re-usable display unit.

Current guidelines direct clinicians to offer a choice between TP or IPC based on patient preference, given the equivalent efficacy of these approaches in two randomised controlled trials.[3] However, this apparent equivalence cannot be generalised to patients with NEL, since the incidence of NEL was extremely low in these important studies, occurring in only 3/54 (6%) and 2/72 (3%) patients in TIME-2 and AMPLE, respectively.[4 5] In clinical practice, the incidence of NEL is almost certainly higher; in audit data recently reported by our unit, NEL was identified in 15/65 patients with MPE (23%) who underwent complete pleural fluid drainage.[6] In this series, NEL was also associated with a twofold to fourfold increase in all-cause mortality, which may explain the under-representation of NEL in the TIME-2 and AMPLE studies.[6]

In our view, the ideal MPE treatment pathway would incorporate an initial functional assessment to determine the probability of underlying NEL, given the profound impact this has on the decision-making required by current guidelines (TP or IPC). Such a pathway, if accurate and efficient, would maximise patient choice in those with expansile lung (who could reasonably choose between TP and IPC) and minimise the rate of futile TP attempts in patients with NEL (avoiding the associated risks, cost and inconvenience). The current randomised feasibility pre-EDIT trial has been initiated to assess the feasibility and inform the design of a future randomised phase III trial testing the efficacy of elastance-directed IPC or TP (EDIT) management. Pre-EDIT also includes a Treatment Preferences Survey (TPS) to more adequately record patient views regarding decision-making in MPE management.

Rationale for the pre-EDIT trial

Detection of NEL

Using routinely available clinical information NEL cannot be reliably detected prior to complete pleural drainage. A thick visceral peel encasing the lung may be seen on cross-sectional imaging in gross cases but is frequently absent. Following diagnostic or therapeutic pleural fluid aspiration, an *ex-vacuo* (hydro-) pneumothorax may be visible.[2] However, this is also an insensitive sign, since a NEL may re-expand enough to appear expansile after removal of currently recommended volumes of fluid (< 1.5 litres). Even after complete drainage of MPE, we have recently reported considerable interobserver variation in radiographic detection of NEL.[6] Sonographic findings, including heavy septation or visceral pleural thickening,[7] or abnormal M-mode and speckle-tracking end-points,[8] have recently been reported as potential NEL biomarkers, but have yet to be validated in large cohorts. Development of a reliable predrainage biomarker for NEL is therefore urgently required.

Pleural elastance (P_{EL}) is an intrinsic property of the pleural cavity and is defined following thoracentesis by the change in intrapleural pressure (ΔIPP) divided by the change in pleural cavity volume, which is assumed to be equal to the volume of fluid removed (ΔV_{OUT}).[9] In previous observational studies, elevated P_{EL} has been strongly associated with the presence of NEL and the occurrence of TP failure.[10] However, previous studies have not attempted to allocate patients to TP or IPC using P_{EL} measurements. For this to be feasible, safe and reliable, various technical difficulties regarding IPP measurement need to addressed, in addition to pathway and trial design issues that are summarised below.

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. In conjunction with Rocket Medical (UK), we have developed a novel, single-use, CE-marked digital pleural manometry (DPM) catheter which allows continuous IPP measurement during thoracentesis (see figure 1). IPP is measured once per second and is mechanically damped via the narrow independent lumen linking the pleural cavity to the electronic transducer (ET). IPP is also temporally damped by displaying a mean IPP on a re-usable digital display unit, based on the preceding 5 s of data. The precision and accuracy of the electronic transducer within the catheter has been 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 and −30 cmH_2O. The manometer was EMC tested and passed BS EN 60601-1-2:2015 and BS EN 60601-1:2006+A1:2013.

EDIT pathway design

Monophasic vs biphasic NEL and selection of an abnormal P_{EL} threshold

Previous studies have reported characteristic patterns of IPP change in patients with NEL and expansile lung, during thoracentesis.[9 11 12] Expansile lung is typically associated with a small linear reduction in IPP over the course of a large volume pleural aspiration. In contrast, NEL results in much larger fall in IPP, reflecting high P_{EL}. This may occur early in the procedure where the aggregated compliance of the lung and parietal structures

is severely limited resulting in a steep linear fall in IPP (monophasic NEL), typically in patients with gross visceral pleural thickening. In more subtle forms of NEL, IPP may initially behave similarly to expansile lung, as the pleural space partially conforms to the volume change and/or the lung expands as much as it can. However, this accommodation will eventually be overwhelmed as the lung reaches its maximum expansion, leading to a fall in IPP, but only after a considerable volume of fluid has been removed. This results in a biphasic P_{EL} curve, which can only be detected if sufficient fluid is removed to reach the relevant inflection point. Importantly, TP success is likely to be reduced in patients with monophasic and biphasic NEL, and the EDIT pathway needs to be capable of detecting both.

In the only previous study that has linked P_{EL} to TP success, Lan *et al* demonstrated that a P_{EL} threshold of ≥ 19 cm H_2O/L following aspiration of 500 mL of pleural fluid was associated with a sensitivity for NEL of 79% (95% CI 0.49 to 0.99).[10] However, the sensitivity of this approach is likely to have been limited by selection of a P_{EL} threshold significantly above the upper limit of normal, which was subsequently defined as 14.5 cm H_2O/L,[13] and the small aspiration volume used (500 mL), which is likely to have been inadequate to detect all cases of biphasic NEL. Adopting a lower P_{EL} threshold and using a larger total aspiration volume may increase the sensitivity of NEL detection, but could potentially sacrifice specificity, particularly if IPP rises transiently due to coughing or unknown measurement artefacts.

Therefore, in the current pre-EDIT trial, we will use a novel definition of NEL, based on a rolling average of P_{EL} recording over the preceding 250 mL fluid removed (P_{EL250}), during a large volume pleural aspiration. The aspiration volume will only be limited by symptoms, a drop in IPP below previously reported safety thresholds or a target pleural effusion depth, based on repeated sonographic measurements (see Methods and analysis section for further detail). IPP pressures used to derive P_{EL} will be consistently measured at end-expiration. NEL will be defined by a maximum P_{EL250} ≥ 14.5 cm H_2O/L (the previously reported upper limit of the normal range for P_{EL})[13] occurring at any point during large volume aspiration. This definition aims to detect NEL at the earliest possible opportunity, including in patients with biphasic NEL, while preserving specificity.

Delivery of elastance-directed management and safety considerations

By definition, the EDIT pathway requires an additional large volume thoracentesis prior to allocation to TP or IPC. If the allocated procedure cannot be delivered promptly, ideally on the same day, this offsets any pathway efficiency gained through detection of NEL. However, placement of 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, thoracic ultrasound (TUS) images will be acquired regularly during aspiration, and the procedure terminated once a minimum safe depth of effusion has been reached (see Methods and analysis section for further details). The protocol also allows that, if required, a 'Boutin-type' needle can employed for pneumothorax induction to ensure safe placement of P_{EL}-allocated IPC or TP. This is regularly practised at level II thoracoscopy centres, including our own, when no, or minimal, pleural fluid is present at local anaesthetic thoracoscopy.[14] However, if the current study finds that this is frequently required to deliver EDIT management, this may impact on the feasibility of subsequent multicentre phase III trial and any subsequent clinical deployment.

Validation of the current definition of P_{EL} using volumetric MRI

P_{EL} is currently defined as ΔIPP (cm H_2O)/ΔV_{OUT} (L), based on the assumption that ΔV_{OUT} is equivalent to the underlying change in pleural cavity volume. However, this assumption may not be valid, due to a combination of air and local anaesthetic introduced during the procedure, variable compliance of the surrounding structures and transient parenchymal-pleural fistulation. Moreover, since ΔIPP describes the aggregated behaviour of a potentially biphasic process, P_{EL} values may inadequately describe pleural physiology in this setting. This uncertainty will be explored in the secondary objectives using volumetric pleural MRI, which allows precise measurement of intrathoracic structures.[15–17]

If the current definition of P_{EL} is validated using MRI, this may enhance the usability of the device used here. In the current protocol, ΔV_{OUT} needs to be manually recorded in parallel with IPP and the data integrated post-procedure. In the future, real-time integration of validated ΔV_{OUT} data with IPP data could facilitate real-time display of P_{EL} (or P_{EL250}), circumventing this time-consuming step. As exploratory objectives, volumetric MRI data will also be correlated with the development of symptoms during thoracentesis, the origin of which are poorly understood.[18]

Treatment preferences survey

All potentially eligible (pre-screened) patients will be asked to complete a TPS (see online supplementary appendix 1). These qualitative data will be of value in deciding whether to pursue future studies of EDIT management and optimising the design of these.

METHODS AND ANALYSIS

Study design and setting

Pre-EDIT is a randomised feasibility trial. Thirty patients with symptomatic MPE will be recruited at a single centre: The Queen Elizabeth University Hospital, Glasgow, UK. Potentially eligible patients will also be identified and pre-screened at Glasgow Royal Infirmary. Patients will be randomised 1:1 to receive either pleural elastance-directed IPC or TP ('EDIT management'), or standard care (placement of an intercostal drain and

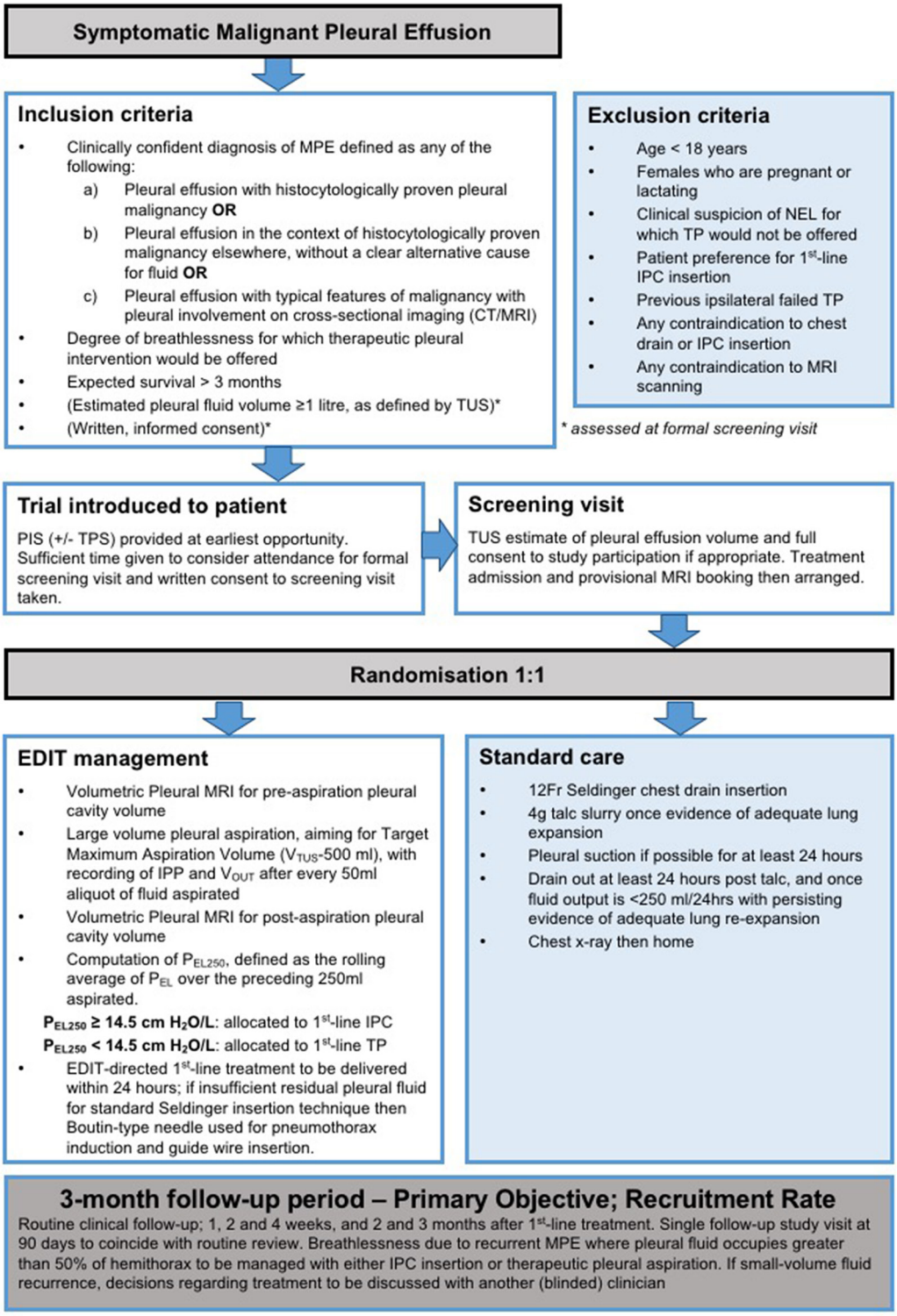

Figure 2 Pre-EDIT trial flow chart. EDIT, elastance-directed intrapleural catheter or talc pleurodesis; IPC, intrapleural catheter; IPP, intrapleural pressure; MPE, malignant pleural effusion; NEL, non-expansile lung; P_{EL}, pleural elastance; TP, talc pleurodesis; TUS, thoracic ultrasound; $\Delta V_{OUT,}$ volume of fluid removed.

attempt at TP). A TPS will be offered to all potentially eligible (pre-screened) patients. The trial is sponsored by National Health Service (NHS) Greater Glasgow & Clyde and jointly funded by Rocket Medical (UK) and The West of Scotland Lung Cancer Research Group. The overall trial design is summarised in figure 2.

Sample size

As a feasibility study, this trial is not subject to a formal sample size estimation. Recruitment of 30 patients is likely to allow a reasonable view of the barriers which might be met in delivering EDIT management, to explore possible solutions, to document the time required to deliver the

procedure and to refine training. Previous estimates of NEL incidence indicate that each arm of the study is likely to contain only a small number of NEL cases which will clearly limit the conclusions that can be drawn regarding the chosen P_{EL250} threshold and MRI data. These have therefore been set as unpowered secondary and exploratory objectives. Instead, a particular focus will be the impact of the study design on recruitment rate, including the requirement for two pleural procedures and randomisation between two treatment arms. This will be assessed by careful review of (pre-) screening logs for consistent reasons for screen failure or unwillingness to participate.

Since pre-EDIT involves novel equipment and imaging protocols, a review of data completeness and quality will be undertaken after completion of TUS assessment, DPM and MRI scanning in the first five patients randomised to EDIT management. This initial experience may be used to refine trial-specific instructions (TSIs) for use in subsequent patients. If significant data are missing or data are of such poor quality as to be uninterpretable from these patients, recruitment may be extended by up to five patients to replace these.

Study objectives and outcome measures

Primary objective

The primary objective is to determine whether it is possible to recruit and randomise 30 patients over 12 months (or 15 patients in any 6-month period). The primary outcome measure will be recruitment rate.

Secondary and exploratory objectives

Secondary objectives and their associated outcome measures are summarised in table 1. Exploratory objectives are described in box 1.

Screening and eligibility assessment

Potentially eligible patients (defined as patients with symptomatic MPE) will be pre-screened by members of the parent clinical teams via cancer multidisciplinary team meetings, routine outpatient appointments and during inpatient reviews. Consecutive pre-screened patients meeting all inclusion criteria and without assessable exclusion criteria will be included in a pre-screening log, provided with a patient information sheet (PIS) at the earliest possible opportunity (see online supplementary appendix 2) and invited to a formal screening visit, during which all eligibility criteria will be assessed (see below). These patients will be given at least 24 hours between provision of the PIS and consent to consider participation.

Inclusion criteria

1. Clinically confident diagnosis of MPE, defined as any of the following:
   a. Pleural effusion with histocytologically proven pleural malignancy OR
   b. Pleural effusion in the context of histocytologically proven malignancy elsewhere, without a clear alternative cause for fluid OR

Table 1 Secondary objectives and associated end points in the pre-EDIT study

Secondary objectives	Secondary end points
To determine the feasibility of P_{EL} computation using the novel DPM	The time taken to perform the EDIT large volume aspiration, including measurement of ΔIPP using the 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 AEs) and SAEs associated with use of the DPM
To assess the pleural fluid aspiration volume required to detect abnormal P_{EL} (where present)	The pleural fluid aspiration volume at which the rolling average pleural elastance over the preceding 250 mL (P_{EL250}) first exceeds the upper limit of normal (14.5 cm H_2O/L)
To determine the proportion of patients allocated to EDIT management who require pneumothorax induction to facilitate safe ICD/IPC insertion following DPM	The proportion of patients in whom pneumothorax induction is required to facilitate safe ICD/IPC insertion in the EDIT arm
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-aspiration minus post-aspiration pleural cavity volume)
To test the accuracy of a predictive model of pleural effusion volume (V_{TUS}) based on 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})

AE, adverse events; DPM, digital pleural manometer; EDIT, elastance-direct intrapleural catheter or talc pleurodesis; ICD, intercostal drain; IPC, indwelling pleural catheter; IPP, intrapleural pressure; P_{EL}, pleural elastance; SAE, serious adverse event; TUS, thoracic ultrasound; V, pleural fluid volume.

Box 1 Exploratory objectives in the pre-EDIT study

- To explore anatomical changes using MRI that may account for the development of symptoms such as chest pain or cough during large volume thoracentesis.
- To explore the factors important to patients with symptomatic malignant pleural effusion when deciding upon first-line definitive pleural intervention.
- To develop a novel predictive model for pleural effusion volume estimation applicable to a wide range of effusion volumes using uniplanar TUS measurement.
- To evaluate the feasibility and potential utility of M-mode assessment of cardiac impulse lung displacement in patients undergoing EDIT management.
- To investigate potential novel MRI biomarkers, such as visceral pleural thickness and parenchymal volume change and strain during respiratory cycle pre-DPM, which may predict NEL.

DPM, digital pleural manometer; EDIT, elastance-direct intrapleural catheter or talc pleurodesis; NEL, non-expansile lung; TUS, thoracic ultrasound.

   c. Pleural effusion with typical features of malignancy with pleural involvement on cross-sectional imaging
2. Degree of breathlessness for which therapeutic pleural intervention would be offered.
3. Age > 18 years.
4. Expected survival > 3 months.
5. Written informed consent.

Exclusion criteria

1. Women who are pregnant or lactating.
2. Clinical suspicion of NEL for which TP would not be offered.
3. Patient preference for first-line IPC insertion.
4. Previous ipsilateral failed TP.
5. Estimated pleural fluid volume ≤ 1 L (defined by TUS).
6. Any contraindication to ICD or IPC insertion, including:
   a. Irreversible coagulopathy.
   b. Inaccessible pleural collection, including lack of suitable IPC tunnel site.
7. Any contraindication to MRI scanning, including:
   a. Claustrophobia.
   b. Cardiac pacemaker.
   c. Ferrous metal implants or retained ferrous metal foreign body.
   d. Previously documented reaction to Gadolinium-containing intravenous contrast agent.
   e. Significant renal impairment (estimated glomerular filtration rate < 30 mL/min).

Informed consent

Consent will be a two-step process. Pre-screened patients, potentially agreeable to trial involvement will be invited to a formal screening visit, during which a member of the research team will discuss the trial and seek written consent to formal screening (see online supplementary appendix 2). This will involve formal assessment of all eligibility criteria, including a bedside TUS for measurement of pleural effusion volume (V_{TUS}). Patients attending a screening visit will be added to a screening log. Patients meeting all eligibility criteria will be asked to give written consent to trial enrolment and randomisation.

Treatment preferences survey

All pre-screened patients will be eligible and asked to participate in the TPS, irrespective of whether they meet all eligibility criteria and/or wish to participate in the main trial. Pre-screened patients will be provided with a separate TPS PIS (see online supplementary appendix 3) and will be given sufficient time, based on their own judgement, to consider participation before signing a separate consent form for involvement in the TPS (see online supplementary appendix 3).

Trial interventions

The trial interventions are summarised in figure 2 and described in detail below. Further information, in the form of TSIs for all interventions are available in online supplementary appendices 4–9.

Baseline assessments

Following consent, elective hospital admission and baseline assessment will be completed by a member of the trial team. The following data will be recorded prior to randomisation:

1. Patient demographics and physical characteristics.
2. Mode of presentation, current diagnosis and smoking history.
3. Eastern Cooperative Oncology Group performance status.
4. Medical history and current medication.
5. Previous pleural interventions.
6. Symptoms, including pain and breathlessness according to 100 mm visual assessment (VA) scores.
7. Results of routine haematological and biochemical tests (within 10 days).
8. Baseline TUS findings.

Randomisation

Immediately after baseline assessment, patients will be randomised 1:1 and allocated using random permuted blocks to either EDIT management or standard care. A validated online system will be used (www.sealedenvelope.com). The availability of potential minimisation factors for the subsequent phase III EDIT trial will be recorded but not used in randomisation, including the LENT prognostic score.[1] The allocated management strategy will commence within 72 hours of randomisation.

Standard care

Following procedure-specific written consent, a 12Fr intercostal drain will be placed to facilitate passive fluid drainage at a rate not exceeding 1000 mL/hour. Chest

radiographs (CXRs) will be performed post-ICD insertion and repeated every 18–24 hours following insertion. Four grams of sterile talc will be administered as a slurry, if there is no evidence of NEL or significant residual pleural fluid, as per existing guidelines.[2] The intercostal drain will be removed once fluid output falls below 250 mL in the preceding 24-hour period, in the presence of a patent drain.

Where NEL or residual fluid is identified, drain patency will be assessed by flushing. Thoracic suction may be applied at the discretion of the primary physician. An additional CXR will be repeated after a further 18–24 hour period. Talc slurry will be administered once at least 50% re-apposition of the visceral and parietal pleural is achieved, based on visual CXR estimation, as per existing guidelines.[2] If this is not achieved within 48 hours of drain placement, further management will be at the discretion of the primary physician. Further details are given in online supplementary appendix 4.

EDIT management

MRI scanning prior to large volume pleural fluid aspiration and P_{EL} assessment

Patients will be scanned using a 3.0T Siemens Prisma MRI scanner. The affected thoracic cavity will be 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 will be acquired as a set of short breath-holds. Time-resolved 3D MR imaging of the complete thorax will then be obtained during tidal free-breathing and maximal inspiratory/expiratory efforts. A modified time-resolved angiography with interleaved stochastic trajectories (TWIST) sequence will be used for this purpose. Following this, Gd-DTPA contrast (Gadovist) will be administered as a 15–40 mL bolus (0.05 mmol/kg). VIBE sequences will be reacquired at copied slice positions to provide comparative postcontrast images at multiple time points.[19] Further scanning details are given in online supplementary appendix 5.

Thoracic ultrasound

Following MRI scanning, a TUS scan will be performed. This will allow the operator to identify a safe site for insertion of the digital pleural manometry catheter, where possible, in the posterior axillary line in the second rib space above the costophrenic angle. Deviation from this site will be recorded. For assessment of the secondary objectives, measurement of the lateral, posterior and median subpulmonic effusion heights in centimetres (LH, PH and SH) will be performed with the patient sitting upright at 90°. The total pleural effusion volume (in millilitres) will be estimated using the Goecke formula (V_{TUS} = (LH +SH) x 70).[20] For examination of the exploratory objectives (see box 1), M-mode measurements of the atelectatic lower lobe will also be acquired, during a breath hold at end-expiration.

Large volume pleural fluid aspiration and computation of P_{EL} (P_{EL250})

After infiltration of the insertion site with local anaesthetic, the digital pleural aspiration catheter will be inserted at the site marked using TUS. Pleural fluid will be removed in 50 mL aliquots until any of the following occur:

- The patient develops chest discomfort or excessive coughing.
- An intrapleural pressure of ≤ −20 cmH_2O is reached.
- The target maximum aspiration volume is reached (horizontal costal to visceral pleural distance ≤ 30 mm).

Sequential end expiratory IPP measurements will be recorded after each 50 mL aliquot. Additionally, the highest and lowest IPP values recorded during maximal respiratory manoeuvres at 200, 500 and 1000 mL will be recorded. Postprocedure, P_{EL250} values will be calculated summarising P_{EL} over the preceding 250 mL of fluid removed. The first P_{EL250} value will therefore be computed based on the IPP change between 0 and 250 mL divided by 0.25. Equivalent P_{EL250} values will then be computed after each subsequent 50 mL fluid removed. Thus, after 300 mL has been removed, the next P_{EL250} value will be computed using the IPP change between 50 and 300 mL, again divided by 0.25. The highest recorded P_{EL250} in each case ($MaxP_{EL250}$) and total pleural fluid volume removed will be recorded. Further details are given in online supplementary appendix 6.

MRI scanning after large volume pleural fluid aspiration and P_{EL} assessment

Following DPM, a further thoracic MRI scan will be performed. Identical T1-weighted VIBE and TWIST sequences will be acquired; however, further intravenous contrast will not be administered.

Allocation and delivery of P_{EL}-directed management

Participants will be allocated to IPC or an ICD and attempt at TP based on their highest recorded P_{EL250} in each case ($MaxP_{EL250}$), as follows:

$MaxP_{EL250}$ ≥ 14.5 cm H_2O/L: allocated to IPC

$MaxP_{EL250}$ < 14.5 cm H_2O/L: allocated to ICD and an attempt at TP

The allocated procedure must be completed within 24 hours of large volume pleural fluid aspiration and computation of P_{EL}. Both will be performed using standard Seldinger techniques based on repeat TUS assessment, unless there is insufficient residual fluid left for this purpose (in the judgement of the operator). In this situation, a 'Boutin-type' needle may be used to obtain blunt access to the pleural cavity and create an iatrogenic (hydro-) pneumothorax for the purpose of safe drain insertion. The remainder of the ICD/IPC insertion will then proceed in the usual fashion. A CXR will be performed postprocedure to assess the drain position. Further detail is provided in online supplementary appendices 7–9.

Management following P_{EL}-directed IPC or intercostal drain insertion

Patients allocated to IPC placement will be managed using standard local policies, as detailed in the TSI (see online supplementary appendix 9). For patients allocated to intercostal drain insertion and TP, postinsertion management will be identical to patients receiving standard care.

Data collection and study visits

VA scores

VA scores for chest pain and breathlessness will be documented at baseline and then daily for 7 days following ICD or IPC placement. Following this, VA scores will be performed weekly until the 28-day clinical follow-up appointment.

Study follow-up visits

Routine clinical appointments are planned for all patients at approximately 7, 28, 60 and 90 days after discharge. A single-study-specific follow-up visit at 90 days (±10) will coincide with routine follow-up where possible. At this visit, a CXR will be acquired and details of hospital admissions, repeat pleural interventions, clinic visits and survival status shall be recorded based on clinical history, augmented by electronic records systems. Where patients are unfit or unable to attend clinic, or have died, these data shall be recorded using electronic systems.

Further pleural intervention

In the event of hospital readmission, further pleural procedures will not be restricted by study participation. Where a gradual return of breathlessness is encountered during follow-up, the research team will assess the likely cause. IPC complications such as infection or blockage will be managed at the discretion of the primary physician. If recurrent MPE is identified following TP and occupies greater than an estimated one-third of the hemithorax on CXR, IPC insertion or therapeutic pleural aspiration will be offered if clinically appropriate. Intervention for smaller volume MPE recurrence will be offered where treatment consensus is achieved with a second respiratory physician blinded to trial group allocation. In the event of disagreement, a third (blinded) casting opinion will be sought.

Data management

Study data will be recorded on paper case report forms and securely transferred to the Queen Elizabeth University Hospital Clinical Research Facility and entered into a trial database. All CXR, CT and MRI images relating to trial participation will be securely stored on NHS systems in line with routine clinical practice. Representative TUS images and M-mode cine clips will be stored on an encrypted trial hard drive.

Statistical analysis plan

The primary objective of trial recruitment will be expressed as a mean monthly rate over the complete trial period and over each 6-month period during which the trial is open. The time taken to perform digital pleural manometry, its failure rate, the incidence of adverse events (AEs) and serious adverse events (SAEs) associated with EDIT management, the number of patients requiring a Boutin needle for ICD/IPC insertion and aspiration volume required to detect abnormal P_{EL} will be reported by simple descriptive statistics or proportions where appropriate. Differences in mean/median values will be assessed using Students t-test or Wilcoxon rank test. Pearson χ^2 test and exact 95% CIs will be used to compare proportions. A standard significance level of 0.05 will be used. The Bland-Altman method will be used to assess agreement between ΔV_{OUT} and ΔV_{MRI} measurements and between preaspiration V_{TUS} and V_{MRI} measurements.

End of trial

Trial recruitment commenced on 28 August 2017 and will terminate on 28 August 2018 or after 30 patients have been recruited, whichever is soonest. Trial participation will cease once the final patient has completed their 90-day follow-up.

Changes to the study protocol since trial opening

The protocol described accurately reflects V.2.5 of the protocol, dated 15 December 2017. The protocol history is summarised below:

V.2.0, dated 4 March 2017

- At request of REC, recruitment process modified such that follow-up contact to invite for screening visit to be made by clinical nurse specialist rather than research team.

V.2.1, dated 5 April 2017

- References to 'Boutin needle' changed to 'Boutin-type needle'.
- Randomisation process changed from minimisation using LENT score to simple random 1:1 allocation with recording of availability of LENT score to assess feasibility of minimisation by LENT in future EDIT trial.

V.2.2, dated 11 May 2017

- Introduction of 5-patient 'run-in' period to allow refinement of TUS, DPM and MRI protocols and assessment of data completeness.
- Removal of statement committing to guidewire placement down Boutin-type needle (where used).
- Removal of statement committing to pneumothorax induction in endoscopy suite.

V.2.3, dated 4 August 2017

- Extension of time allowed between randomisation and delivery of intervention from immediate to up to 72 hours.

V.2.4, dated 9 October 2017

- Remove preprocedure TUS-estimated target volume as stop criterion for DPM and replace this with target horizontal costal-visceral pleural distance on TUS assessment at intervals during the aspiration procedure.
- Removal of 2-week follow-up appointment.
- Follow-up interval to start from date of discharge rather than date of procedure.

V.2.5, dated 15 December 2017

- Recording of pre-screened patients.
- Introduction of TPS.

ETHICS AND DISSEMINATION

Safety reporting

Details of any AEs or SAEs will be collected during routine and trial follow-up visits. All AEs and SAEs will be recorded in the patient's medical records and reported to the trial sponsor.

Dissemination

Pre-EDIT, and the ultimate intention to definitively evaluate EDIT management if found to feasible, will be publicised at regional and national meetings. The results of pre-EDIT trial will be presented at scientific meetings and published in peer-reviewed journals.

Trial management

A Trial Management Group consisting of the chief investigator, clinical research fellow, lead trial research nurse, statistician and administrative assistant will oversee the running of the trial and meet on a monthly basis.

Contributors GAM: contribution to the conception and design of the work, data acquisition, analysis and interpretation of data for the work; drafting the work. GAM, ST, ACK, JEF, PM, AC, KGB: final approval of the version to be published; agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. ST: contribution to the conception and design of the work and interpretation of data for the work. ST, ACK, JEF, PM, AC, KGB: revising the work critically for important intellectual content; final approval of the version to be published. ACK: contribution to the design of the work and data acquisition for the work. JEF: contribution to the design of the work, data acquisition, analysis, and interpretation of data for the work. PM: contribution to the design of the work, analysis and interpretation of data for the work. AC: contribution to the design of the work. KGB: principal contribution to the conception and design of the work; data acquisition, analysis and interpretation of data for the work

Funding This work was supported by Rocket Medical (UK) and the West of Scotland Lung Cancer Research Group (Award September 2015). KGB is part-funded by NHS Research Scotland.

Competing interests Rocket Medical (UK) have part-funded this work and will supply the digital pleural manometry equipment to be used in the study.

Patient consent Not required.

Ethics approval Pre-EDIT was approved by the West of Scotland Regional Ethics Committee on 8 March 2017 (Ref: 17/WS/0042).

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Clive AO, Kahan BC, Hooper CE, *et al*. Predicting survival in malignant pleural effusion: development and validation of the LENT prognostic score. *Thorax* 2014;69:1098–104.
2. Roberts ME, Neville E, Berrisford RG, *et al*. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010;65(Suppl 2):ii32–40.
3. Simoff MJ, Lally B, Slade MG, *et al*Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines*Chest* 2013;143:e455.
4. Davies HE, Mishra EK, Kahan BC, *et al*. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA* 2012;307:2383–9.
5. Thomas R, Fysh ETH, Smith NA, *et al*. Effect of an Indwelling Pleural Catheter vs Talc Pleurodesis on Hospitalization Days in Patients With Malignant Pleural Effusion: The AMPLE Randomized Clinical Trial. *JAMA* 2017;318:1903–12.
6. Martin GA, Kidd AC, Tsim S, *et al*. S26 Identification and prognostic importance of non-expansile lung following drainage of suspected malignant pleural effusion. *BMJ Publishing Group Ltd and British Thoracic Society* 2017:A19–A20.
7. Huggins JT, Sahn SA, Heidecker J, *et al*. Characteristics of trapped lung: pleural fluid analysis, manometry, and air-contrast chest CT. *Chest* 2007;131:206–13.
8. Salamonsen M, Ware R, Fielding D. A new method for performing continuous manometry during pleural effusion drainage. *Respiration* 2014;88:61–6.
9. Light RW, Jenkinson SG, Minh VD, *et al*. Observations on pleural fluid pressures as fluid is withdrawn during thoracentesis. *Am Rev Respir Dis* 1980;121:799–804.
10. Lan RS, Lo SK, Chuang ML, *et al*. Elastance of the pleural space: a predictor for the outcome of pleurodesis in patients with malignant pleural effusion. *Ann Intern Med* 1997;126:768–74.
11. Huggins JT, Doelken P, Sahn SA. The unexpandable lung. *F1000 Med Rep* 2010;2:77.
12. Huggins JT, Doelken P, manometry P*Clin Chest Med* 2006;27:229–40.
13. Heidecker J, Huggins JT, Sahn SA, *et al*. Pathophysiology of pneumothorax following ultrasound-guided thoracentesis. *Chest* 2006;130:1173–84.
14. Rahman NM, Ali NJ, Brown G, *et al*. Local anaesthetic thoracoscopy: British Thoracic Society Pleural Disease Guideline 2010. *Thorax* 2010;65(Suppl 2):ii54–60.
15. Childs H, Ma L, Ma M, *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* 2011;13:40.
16. Meerang M, Boss A, Kenkel D, *et al*. Evaluation of imaging techniques for the assessment of tumour progression in an orthotopic rat model of malignant pleural mesothelioma†. *Eur J Cardiothorac Surg* 2015;47:e34–41.
17. Nelson AJ, Worthley MI, Psaltis PJ, *et al*. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Reson* 2009;11:15.
18. Feller-Kopman D, Walkey A, Berkowitz D, *et al*. The relationship of pleural pressure to symptom development during therapeutic thoracentesis. *Chest* 2006;129:1556–60.
19. Tsim S, Humphreys CA, Cowell GW, *et al*. Early Contrast Enhancement: A novel magnetic resonance imaging biomarker of pleural malignancy. *Lung Cancer* 2018;118:48–56.
20. Goecke W, Schwerk WB. Die diagnostishce Wertigkeit der Sonographie in der Identifikation von Pleuraergussen im Vergleich zur konventionellen Rontgen-Thoraxaufnahme. In: G J, BJ H, von KG, eds. *Ultraschalldiagnostik*. Berlin/Heidelberg/New York/Tokio, 1990:385–7.