**A Feasibility Study Evaluating the Efficacy of Indwelling Pleural Catheters Plus Sclerosant in Persistent Symptomatic Pleural Effusions Secondary to Heart Failure**

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**This protocol has regard for the HRA guidance**

**RESEARCH REFERENCE NUMBERS**

|  |  |
| --- | --- |
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| **REC reference** | 21/LO/0490 |
| **ISRCTN Number / Clinical trials.gov Number:** | **TRIAL REGISTRY NUMBER AND DATE - TBC** |
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| **FUNDERS Number:** | 61784695 |

1. SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor’s (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

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1. LIST OF ABBREVIATIONS

AE Adverse Event

AR Adverse Reaction

BD Becton, Dickenson and Company

CA Competent Authority

CI Chief Investigator

CFS Clinical Frailty Score

CRF Case Report Form

CTIMP Clinical Trial of Investigational Medicinal Product

DMC Data Monitoring Committee

EC European Commission

EU European Union

GCP Good Clinical Practice

GMP Good Manufacturing Practice

IB Investigator Brochure

ICF Informed Consent Form

ICH International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

IMP Investigational Medicinal Product

ISF Investigator Site File (This forms part of the TMF)

ISRCTN International Standard Randomised Controlled Trials Number

MA Marketing Authorisation

MHRA Medicines and Healthcare products Regulatory Agency

MS Member State

MLHFQ Minnesota Living with Heart Failure Questionnaire

NIMP Non-Investigational Medicinal Product

NYHA New York Heart Association functional classification

NHS R&D National Health Service Research & Development

PI Principal Investigator

PA Postero-anterior

PIC Participant Identification Centre

PIS Participant Information Sheet

QA Quality Assurance

QC Quality Control

RCT Randomised Control Trial

REC Research Ethics Committee

REDCap Research Electronic Data Capture system

SAE Serious Adverse Event

SAR Serious Adverse Reaction

SDV Source Data Verification

SOB Shortness of Breath

SOP Standard Operating Procedure

SmPC Summary of Product Characteristics

SSI Site Specific Information

SUSAR Suspected Unexpected Serious Adverse Reaction

TMF Trial Master File

TMG Trial Management Group

TSC Trial Steering Committee

VAS Visual Analogue Scale

1. TRIAL SUMMARY

|  |  |
| --- | --- |
| Trial Title | A Feasibility Study Evaluating the Efficacy of Indwelling Pleural Catheters Plus Sclerosant in Persistent Symptomatic Pleural Effusions Secondary to Heart Failure |
| Internal ref. no. (or short title) | REDUCE 2 |
| Clinical Phase | Phase III feasibility |
| Trial Design | Randomised, non-blinded feasibility study |
| Trial Participants | Patients with recurrent pleural effusions that, in the opinion of the treating physician, are secondary to heart failure and are non-responsive to standard medical therapy |
| Planned Sample Size | 40 patients |
| Treatment duration | Treatment administered as a single dose |
| Follow up duration | 12 weeks |
| Planned Trial Period | 2 year recruitment period |
| Feasibility Question | The primary objective of the REDUCE 2 trial is to assess the feasibility of delivering a randomised trial of IPC insertion and talc sclerosant instillation compared to recurrent pleural aspiration alone (standard care) in patients with cardiogenic pleural effusions. This will be assessed by the number of participants recruited and successfully randomised in the 2 year recruitment period. In order to demonstrate feasibility, the absolute number recruited would need to be at least 80% of target (i.e. recruit at least 32 within the specified timeframe) and if ≥50% eligible patients are successfully randomised. |
| Exploratory Outcomes | 1. Does using talc and an IPC together reduce the time to pleurodesis compared to standard care? 2. Does using talc and an IPC together alter the amount of pain and breathlessness a patient experiences when compared to standard care? 3. Does the use of talc and an IPC together alter a patient’s quality of life, when compared to standard care? 4. What are the logistical and clinical difficulties with using the novel protocol in this patient group? 5. Does the combination of talc and an IPC together influence the degree of fluid septation and loculation seen on thoracic ultrasound? 6. Does the baseline level of serum brain natriuretic peptide (NT pro-BNP) correlate with the volume of pleural fluid drained and chance of successful pleurodesis? 7. Does talc in combination with IPC affect healthcare utilisation compared to standard care? 8. Does talc in combination with IPC affect adverse events rates compared to standard care? 9. Which are the most appropriate outcome measures to use to assess the proposed hypothesis of the full scale trial and the secondary outcome measures of this feasibility trial? |
| Non-Investigational Medicinal Product(s) | Medical Talc (*Steritalc,* Novatec) & Lidocaine |
| Formulation, Dose, Route of Administration | 4 grams of talc administered intrapleurally as a slurry with normal saline and 3mg/kg dose of Lidocaine 1% w/v solution for injection administered intrapleurally prior to receiving talc slurry. |

1. FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER** | **FINANCIAL AND NON FINANCIAL SUPPORT GIVEN** |
| Becton, Dickinson and Company,  1 Becton Drive,  Franklin Lakes,  New Jersey 07417 USA | Grant of £179,827  PleurX Pleural Catheter Mini kits  PleurX Drainage bottles |

1. ROLE OF TRIAL SPONSOR AND FUNDER

The sponsor and funder have no role or remit in the trial design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

1. ROLES AND RESPONSIBILITIES OF TRIAL MANAGEMENT COMMITEES/GROUPS & INDIVIDUALS

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Trial Steering Committee/ Data Monitoring Committee

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Chief Investigator Professor Nick Maskell

Trial Co-ordinator Dr Hugh Welch

Lead Trial Nurse Mrs Sonia Patole

Trial Statistician Dr Paul White

Co-investigator Dr Rahul Bhatnagar

Co-investigator Professor Najib Rahman

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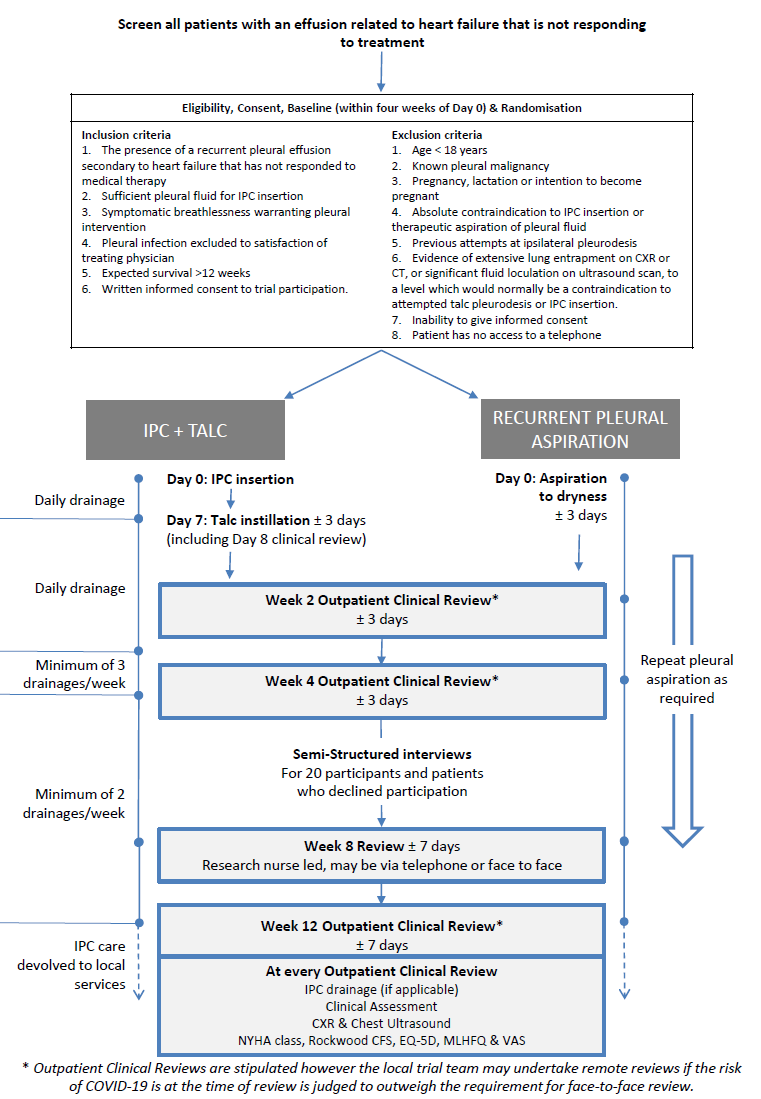
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| 1. KEY WORDS: | Non-malignant pleural effusion  Heart failure  Indwelling pleural catheters  Talc pleurodesis  Aggressive drainage  Therapeutic aspiration |

2. TRIAL FLOW CHART



1. BACKGROUND

Heart failure is a hugely important disease globally, with a prevalence of over 5.8 million in the USA alone, and 23 million worldwide [1]. Up to 500,000 patients with heart failure will develop a pleural effusion every year in the USA [2], and over 70% of all heart failure patients will develop a pleural effusion at some point in their disease course [3]. The socioeconomic burden of disease is high and effective medical interventions have the potential to benefit many patients.

The pathophysiology of the heart failure related pleural effusion is a topic of ongoing debate. In health, pleural fluid is predominantly produced and resorbed by the parietal pleura as a result of filtration from the systemic circulation [4]. In heart failure, which may be driven by systolic or diastolic dysfunction, valvular heart disease or constrictive heart disease [5], it is proposed that, the systemic pressure rises, resulting in a greater volume of filtered fluid entering the pleural space from the parietal pleura [4]. This may be compounded by a reduction in the lymphatic drainage of the pleural space resulting from increased venous pressure. Increased pulmonary pressures may also lead to effusion formation by alveolar oedema formation driven by pulmonary venous hypertension. This may lead to fluid filtration across the visceral pleura into the pleural space [4, 6]. This model has been corroborated by a study of patients with CHF related pleural effusions which found that 57% demonstrated significantly elevated pulmonary capillary wedge pressures [7].

Heart failure related pleural effusions are most commonly transudates, especially in a state of acute volume overload [3]. However, chronicity and diuretic therapy may result in the transformation of a transudate into an exudate [8].

The first line of management for pleural effusions secondary to heart failure is medications to optimise cardiac function and diuretics, such as furosemide. Whilst the majority of patients improve with medications, 10% of these patients have effusions which are refractory to medical management [5]. Additionally, the high diuretic dosages used in the pursuit of reducing the size of pleural effusion and improving symptoms can lead to significant side-effects, including acute kidney injury, electrolyte disturbances and hypotension. The presence of a refractory pleural effusion in patients with CHF has been found to denote a 50% 1-year mortality [9]. Recurrent pleural aspiration forms the current mainstay of treatment for these patients. Patients may also undergo chest tube insertion should large volume drainage be indicated. However, repeated pleural interventions confer associated risks of pain, bleeding, infection and other complications [10]. Additionally, they often only provide transient symptom relief. Thoracentesis and chest tube insertion is increasingly complicated by the fact that many of patients are on a form of oral antiplatelets or anticoagulation, which increase procedural risks.

An alternative approach is to instil a sclerosant agent, such as medicinal talc, into the pleural space via chest tube to provoke inflammation and thereby induce permanent apposition of the pleural membranes. This technique usually necessitates a hospital admission and inpatient stay of three to five days [11-13]. One retrospective study of patients with effusions secondary to CHF demonstrated a 75% success rate with talc slurry [12]. However, it was limited by small sample size of 16, and variable follow-up, ranging from two months to three years. Although commonly used for malignant pleural effusions, chemical pleurodesis is used relatively rarely for the management of heart failure related effusions, and this is reflected in the paucity of evidence on the subject. One possible explanation for this that many patients with these effusions are not managed by specialist pleural physicians.

This patient cohort have a poor prognosis, with a median life expectancy of one year and the presence of an effusion requiring aspiration is a marker of severe disease and poor prognosis [9]. The median survival in these patients was not dissimilar to some malignancies, and it supports the idea that these patients should be managed with a symptoms-based approach, and every effort should be made to minimise possible hospital length of stay.

Indwelling pleural catheters have been shown to be an effective method of controlling pleural effusions in malignant disease in several robust randomised control trials [14-16]. Observational data has also supported their use in non-malignant effusions with observational studies examining their use in heart failure. Herlihy et al published the first case series on the use of Pleurx® IPC in 5 patients with refractory pleural effusions secondary to CHF, finding that the catheter effectively controlled the effusions and symptoms [17]. However, two patients developed pleural infection, one of which died of resultant sepsis. Srour et al published a prospective study in patients with cardiogenic pleural effusions, inserting 43 IPCs in 38 patients [18]. This study demonstrated an improvement in breathlessness and demonstrated a proportion of these patients (29%) achieved spontaneous pleurodeses. Two patients required IPC re-insertion: one due to a leaking IPC valve and the second due to IPC removal for a diagnostic thoracoscopy. A further three patients went on to have contralateral IPC insertion due to the development of bilateral pleural effusions. The study protocol was careful to minimise catheter infections, with drainages performed by trained home-care personnel and close outpatient monitoring, which may partially explain why there were no incidences of empyema. Freeman et al performed a retrospective cohort analysis on 80 patients with recurrent cardiogenic effusions, with 40 patients receiving talc poudrage and 40 patients IPCs [11]. They determined adequacy of palliation based on reintervention rates, with similarly low reintervention rates in in the poudrage cohort (5%) as the IPC group (2.5%). The hospital length of stay was significant shorter and the readmission and complication rate lower in the IPC cohort. No incidences of pleural infection were reported in either group.

In a retrospective cohort study Majid et al examined 36 patients with cardiogenic effusions [19]. 15 patients were managed with thoracoscopy followed by talc poudrage and IPC placement (Group 1) and 26 patients having IPC placement alone (Group 2). Pleurodesis rates were higher in Group 1, with 80% achieving pleurodesis at a median time 11.5 days, compared to a 25% pleurodesis rate at a median time of 66 days in Group 2. The shorter time to pleurodesis and subsequent drain removal likely reduced the risk of IPC infection, with only two cases of pleural infection, both of which occurred in Group 2. Seven patients also underwent contralateral IPC placement due to development of bilateral pleural effusions.

A systematic review of 13 studies concluded that IPCs are effective and a viable option in the management of patients with refractory benign pleural effusion [20]. The REDUCE trial (IRAS 151804), a multicentre randomised controlled trial which recently completed recruitment, randomised patients with refractory effusions secondary to heart, liver and renal failure between IPCs and therapeutic aspiration. Initial results show that IPCs were well tolerated in the cardiac subgroup with minimal complications.

The role of the IPC has evolved recently, from use solely as a drain, to an active participant in the management of pleural disease. It is recognised that patients with IPCs will achieve self-pleurodesis, with 42% of patients with IPCs for heart failure achieving self-pleurodesis [20]. This allows for catheter removal thereby rendering the patient free of both pleural effusion and IPC. However, the mean duration for pleurodesis in CHF ranges from 56 to 150 days [11, 21] and with a median survival of one year, there is incentive to achieve a more rapid pleurodesis.

Combining IPC insertion with talc instillation could potentially result in faster and more reliable pleurodesis and therefore IPC removal. The IPC Plus study demonstrated this pathway to be safe and effective in patients with malignant disease, showing significant higher rates of pleurodesis in the talc arm (43%) at day 35 compared with 23% in the placebo group, with no difference in mortality, adverse events or days in hospital [22].

A further recent development in the malignant pleural effusion population has been the advent of ‘aggressive’ or daily IPC drainage following insertion. Common practice has been to drain IPCs initially three times per week following insertion, and to then tailor the drainage frequency to the individual patient’s requirement. More recently however, the concept of draining the pleural space to dryness and then keeping it as dry as possible to promote pleurodesis has been explored by two randomised trials [23, 24]. Both studies have shown that aggressive drainage results in higher and more rapid rates of autopleurodesis. Rates of adverse events were similar across both arms in both studies.

Therefore, an ideal approach to the management of refractory CHF related pleural effusions should be the combination of talc instillation, IPC insertion and aggressive drainage. This could result in more rapid pleurodesis and therefore freedom from catheter, thus relieving the patient’s symptom burden and improving their quality of life. As the patient may no longer require recurrent therapeutic pleural aspirations, there are also potential health economic benefits from this approach. Should pleurodesis fail, the IPC should be able to provide symptomatic relief from recurrence of the pleural effusion.

No studies to date have examined this combined management strategy in patients with pleural effusions secondary to heart failure.

In order to assess the effects of this protocol, both objective clinical measures and more subjective records of the participant experience are required. REDUCE 2 will measure clinical outcomes including volume of pleural fluid drained/aspirated, chest x-ray appearances and thoracic ultrasound appearances. NYHA functional classification [25], well established and used by heart failure clinicians, will be used to assess reported functional capacity throughout the study period. To further broaden the cross-specialty interpretability, the Rockwood Clinical Frailty Score (CFS), a well-validated clinical measure of susceptibility to poor outcomes will be assessed by clinicians throughout the study [26, 27]. This score uses daily activities to define clinical frailty and is commonly employed by geriatricians, acute physicians and, increasingly, cardiologists as a marker of frailty and predictor of poor outcomes.

Recent literature related to the management of pleural effusions often uses patient-reported outcome measures (PROMs) such as visual analogue scores (VAS) for breathlessness [28], the Euroqol EQ-5D questionnaire [29], combined with clinical outcomes such as volumes of pleural fluid drained and chest x-ray findings. As patients with refractory CHF related pleural effusions have a 50% 1-year mortality [9], interventions to manage these effusions are palliative in nature. However, there are no PROMs that are specifically developed for the pleural effusion population. Within the sphere of palliative care, various PROMs have been explored but there is no current standardised measure [30]. Within the heart failure population, the Minnesota Living with Heart Failure Questionnaire (MLHFQ) is a well validated tool for assessing the impact of heart failure on a patient’s life [31]. This questionnaire will be used in combination with the EQ-5D to monitor any effect of either study arm on the study participants’ lives.

Qualitative research has gained much traction in recent years in providing patient-centred measures of the efficacy of healthcare interventions [32, 33]. Qualitative research is usually undertaken by means of semi-structured interviews designed to elicit an understanding of patient experiences, perceptions, behaviour, processes and the meanings they attach to them [34]. However, the technique has yet to be applied to the CHF-pleural effusion population. It offers the possibility to gain insights into how every aspect of a healthcare intervention impact on patients and their unique needs. Combing qualitative research with currently used and comparable qualitative PROMs and objective clinical endpoints would give further insights to the true effects of a new intervention such as the IPC, talc and aggressive regimen proposed above.

1. RATIONALE

The IPC PLUS study has shown the efficacy of outpatient talc administration via IPC for malignant pleural effusions [22]. The efficacy of aggressive IPC drainage has also been demonstrated in the malignant population [23, 24]. A randomised trial is therefore needed to test the hypothesis that the combination of an IPC in addition to talc sclerosant and aggressive drainage is superior to current standard care (recurrent therapeutic aspirations) in the management of refractory cardiogenic pleural effusions. The hypothesis would be that the IPC and talc group will achieve pleurodesis faster and in a greater number of patients than the therapeutic aspiration (standard care) group thus palliating symptoms related to pleural effusion, and allowing for catheter removal. Liberty from catheter would increase patients’ quality of life and reduce IPC associated complications and morbidity, such as infection and pain. Given that this would be the first study of its kind in this population, a feasibility trial is required to assess the practicality and accessibility of randomisation of patients to these management arms.

* 1. Assessment and management of risk

The treatments being offered in this trial are all established with acceptable levels of risk in other patient populations. Both IPC insertion and talc pleurodesis are standard care for malignant pleural effusion.

IPCs are an established first line therapy for recurrent malignant pleural effusions. The risks associated with them include: infection, pain, blockage or failure through other means. There are also risks associated with insertion technique which include: pain, bleeding, local trauma, pneumothorax, admission to hospital and procedure failure. Some centres sedate patients for IPC insertion which confers additional risk. The benefits of IPC insertion for pleural effusion are: drainage of pleural fluid with accompanying improvement in symptoms related to fluid, spontaneous self-pleurodesis in some patients and fewer hospital visits for fluid drainage.

Talc pleurodesis is an established therapy usually administered via a chest tube. IPC PLUS demonstrated the efficacy of talc administered via an IPC [22]. The risks associated with talc pleurodesis are (in addition to chest tube or IPC insertion): pain, fever and procedure failure. The benefits associated with talc pleurodesis are: prevention of recurrence of pleural effusion thus reducing associated symptoms and therefore earlier IPC removal.

Aggressive drainage has been shown in two trials not to be associated with a significant increase in adverse event rates compared to standard IPC drainage regimens [23, 24]. The risks associated with daily drainage are: short term inconvenience to patient due to increased healthcare interactions, infection, IPC damage or IPC displacement. The benefits of aggressive drainage are: a higher likelihood of pleurodesis leading to IPC removal and pleurodesis occurring faster than with standard drainage regimens.

It is not anticipated that the heart failure effusion patient group will confer a greater risk than the established malignant pleural effusion patient population for these techniques when used in combination. The only study of IPC use in patients with effusions related to heart, liver and renal failure (REDUCE 1 - 21, 8 and 4 participants respectively – awaiting study publication) showed a similar safety profile to the use of IPCs in the malignant population.

Risks will be assessed and managed via the adverse events recording and reporting process (see Section 9).

The study risk is categorised as Type A (no higher than the risk of standard medical care).

1. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS
   1. Primary feasibility question

The primary objective of the REDUCE 2 trial is to assess the feasibility of delivering a randomised trial of IPC insertion and talc sclerosant instillation compared to recurrent pleural aspiration alone in patients with cardiogenic pleural effusions. This will be assessed by the number of participants recruited and successfully randomised in the 2 year recruitment period. In order to demonstrate feasibility, the absolute number recruited would need to be at least 80% of target (i.e. recruit at least 32 within the specified timeframe) and if ≥50% eligible patients are successfully randomised.

* 1. Exploratory research questions

1. Does using talc and an IPC together reduce the time to pleurodesis compared to standard care?
2. Does using talc and an IPC together alter the amount of pain and breathlessness a patient experiences when compared to recurrent pleural aspirations?
3. Does the use of talc and an IPC together alter a patient’s quality of life, when compared to recurrent pleural aspirations?
4. What are the logistical and clinical difficulties with using this novel protocol in this patient population/across different hospitals?
5. Does the combination of talc and an IPC together in this population influence the degree of fluid septation and loculation seen on thoracic ultrasound?
6. Does the baseline level of serum brain natriuretic peptide (NT pro-BNP) correlate with the volume of pleural fluid drained and rate of successful pleurodesis?
7. Does talc in combination with IPC affect healthcare utilisation compared to recurrent pleural aspirations?
8. Does talc in combination with IPC affect adverse events rates compared to recurrent pleural aspirations?
9. Which are the most appropriate outcome measures to use to assess the proposed hypothesis of the full scale trial and the secondary outcome measures of this feasibility trial?
   1. Primary endpoint/outcome

The primary outcome of the REDUCE 2 trial is the number of participants recruited from those who meet the eligibility criteria. The study will be deemed successful if the absolute number recruited is at least 32, and ≥50% eligible patients are successfully randomised.

* 1. Secondary endpoints/outcomes

1. The number of patients with successful pleurodesis at 4 and 12 weeks post intervention
2. Self-reported quality of life status, measured at baseline, 2 weeks, 4 weeks, and 12 weeks, measured using the EQ5D and MLHFQ
3. Self-reported VAS scores for breathlessness, measured at baseline, and daily for the subsequent 2 weeks then weekly for the remainder of follow up
4. Self-reported VAS scores for chest pain, measured at baseline, and daily for the subsequent 2 weeks then weekly for the remainder of follow up
5. NYHA class at baseline, 2 weeks, 4 weeks, and 12 weeks
6. The number of drainages/procedures per patient per week and total volume of pleural fluid removed
7. All-cause mortality up to 12 weeks post randomisation
8. Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at 2, 4 and 12 weeks post randomisation
9. Number and type of episodes of healthcare utilisation in trial period
10. Adverse events related to trial intervention
11. Protocol deviation rates
12. Data completion rates
    1. Qualitative outcomes

Patient experiences of the trial process using semi-structured interview. Interviews will be undertaken by the central trial team, either via telephone or video calling computer software. Interviews will be audio-recorded.

* 1. Table of endpoints/outcomes

|  |  |  |
| --- | --- | --- |
| **Objectives** | **Outcome Measures** | **Timepoint(s) of evaluation of this outcome measure (if applicable)** |
| **Primary Objective** To assess the feasibility of a full scale clinical trial | Percentage of target (80%) and of eligible (50%) participants that are randomised | 12 weeks |
| **Secondary Objectives** Example: To assess the safety of IPC and talc in patients with recurrent cardiogenic pleural effusions despite optimised medical therapy | The number of patients with successful pleurodesis at 4 and 12 weeks post randomisation | 12 weeks |
| Self-reported quality of life status measured at baseline, 2 weeks, 4 weeks, and 12 weeks post intervention | 12 weeks |
| Self-reported VAS scores for breathlessness, measured at baseline and daily for the subsequent 2 weeks then weekly for the remainder of follow up | 12 weeks |
| Self-reported VAS scores for chest pain, measured at baseline, and daily for the subsequent 2 weeks then weekly for the remainder of follow up | 12 weeks |
| NYHA class at baseline, 2 weeks, 4 weeks, and 12 weeks | 12 weeks |
| The number of drainages/procedures per patient per week and total volume of pleural fluid removed | 12 weeks |
| All-cause mortality up to 12 weeks post IPC insertion | 12 weeks |
| Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at 2, 4 and 12 weeks post randomisation | 12 weeks |
| Number of episodes of healthcare utilisation in trial period | 12 weeks |
| Adverse events related to trial intervention | 12 weeks |
| Protocol deviation rates | 12 weeks |
| Data completion rates | 12 weeks |
| **Exploratory Endpoints** | Patient experiences of the trial process using semi-structured interview | 2-8 weeks |

1. TRIAL DESIGN

The trial is a dual arm, randomised, non-blinded feasibility study.

Participants randomised to the intervention arm will undergo IPC insertion with subsequent aggressive drainage and talc instillation.

Participants randomised to the control arm will undergo an initial therapeutic pleural aspiration to dryness or maximum clinically appropriate volume. Further therapeutic pleural aspirations will be carried out as required on an ad hoc basis. **Participants in this arm may be offered an IPC at the end of the study follow up period at the discretion of local site.**

Follow up will occur over a 12 week period as detailed in sections below.

1. TRIAL SETTING

Patients will be recruited from 12 trial centres in the UK.

Clinical care, IPC insertion and imaging will be provided by local medical professionals at the patients’ base hospital, or appropriate satellite centres. Further care will be provided by ward and specialist nurses in these centres, who will also be available for telephone support. Routine drainage of pleural fluid will take place in the community and at follow-up visits. IPC drainages will be performed by appropriately trained medical staff such as district nurses, specialist nurses or research nurses. If required, training for trial sites and local healthcare staff will be provided by BD.

1. PARTICIPANT ELIGIBILITY CRITERIA
   1. Inclusion criteria
2. The presence of a recurrent pleural effusion secondary to heart failure that has not responded to medical therapy
3. Sufficient pleural fluid for IPC insertion
4. Symptomatic breathlessness warranting pleural intervention
5. Pleural infection excluded to satisfaction of treating physician
6. Expected survival >12 weeks from procedure
7. Written informed consent to trial participation.
   1. Exclusion criteria
8. Age < 18 years
9. Known pleural malignancy
10. Pregnancy, lactation or intention to become pregnant
11. Absolute contraindication to IPC insertion or therapeutic aspiration of pleural fluid
12. Previous attempts at ipsilateral pleurodesis
13. Evidence of extensive lung entrapment on CXR or CT, or significant fluid loculation on ultrasound scan, to a level which would normally be a contraindication to attempted talc pleurodesis or IPC insertion.
14. Inability to give informed consent
15. Patient has no access to a telephone
16. TRIAL PROCEDURES
    1. Recruitment

The recruitment target for this study is 40 patients, who will be randomised in a 1:1 ratio to intervention and non-intervention. Recruitment will occur for 2 years from date of green light of 8th site.

In light of the COVID-19 pandemic, REDUCE 2 may undergo one or more study pauses. In the event of a study pause, the study time limit will be extended appropriately.

* + 1. Participant identification

Suitable patients will be identified from the following sources:

1. Active screening of heart failure MDT lists and clinics
2. Referrals to respiratory services from cardiologists and/or other clinicians
3. Liaison with local heart failure services
4. Routine clinic appointment
5. Inpatient reviews

All patients are envisaged to be referred by healthcare professionals involved in their care and each site will have a representative from cardiac services who will be responsible for identifying patients.

* + 1. Screening

All patients with an effusion related to heart failure that is not responding to treatment will be assessed for eligibility for the REDUCE 2 Trial using the inclusion / exclusion criteria as above. Reasons that patients were not eligible for trial participation or if they were eligible but declined will be recorded throughout the trial.

Patients will have to have undergone relevant medical investigations to meet the inclusion and exclusion criteria. These and are not trial specific procedures but are undertaken as part of normal clinical care and should include (but are not limited to):

1. Chest X-ray (within 10 days)
2. Thoracic ultrasound (within 10 days)
3. Pleural aspiration (most recent, timeframe not specified)
4. ECG (within 1 year)
5. Echocardiogram (within 1 year)
6. Standard blood tests (within 3 months) including BNP
7. NYHA classification

Any of the above investigations that have not been completed prior to screening must be arranged at the screening visit. Screening visits are regarded as standard care.

* + 1. Payment

Travel expenses will be paid for patients attending for trial visits but not standard care clinical review.

Reimbursement will be made to the recruiting site/organisation per patient recruited.

* 1. Consent

Potentially eligible patients will be met by a member of the trial team who will discuss the trial with them. The patients will be given a patient information sheet (PIS). The patients will be given sufficient time to consider whether they would like to be enrolled in the trial before further discussion. If required, potential participants may be given more time and a private space to read, understand and weigh participation. It is suggested that consent should be undertaken at the baseline visit, however an alternate acceptable approach would be to consent and complete the baseline visit at a later date, should the potential participant wish to have longer to make their decision in an unpressurised fashion.

Due to the nature of heart failure-related pleural effusions, it is likely that potential participants will have been aware of their diagnosis for some months or even years prior to being asked to join REDUCE 2. Therefore it is anticipated that participants should not feel overburdened with information pertaining to a new diagnosis and possible entry into a clinical study at the same time.

Should the patient wish to enter the trial, written consent will be taken by a member of the trial team.

Consent will also be taken for entry into the qualitative section of the study at this point (see section 7.9.1). This will include consent for recording of the interview and use of anonymised quotations in the final report and any peer-reviewed literature. However, this can be delayed and rediscussed at a later opportunity if a participant wishes. Consent will be reconfirmed immediately prior to commencement of the interview.

The consenting process will include an assessment of capacity according to the Mental Capacity Act. Patients will be judged to have capacity to consent if they are able to demonstrate they are able to:

* + understand the purpose and nature of the trial
  + understand what the trial involves, its benefits, risks and burdens
  + understand the alternatives to taking part
  + retain the information long enough to make an effective decision.
  + make a free choice
  + make this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)

Trial registration will occur at consent. Registration will be carried out by data entry into the REDCap (Research Electronic Data Capture system hosted by the University of Bristol) web portal. Access to the system is via the internet and all sites will have access. Registration will be confirmed on screen and notification sent contemporaneously to site staff and the central trial management team.

* + 1. Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable

This is at the discretion of the trial site. No mandatory enrolment in ancillary studies is suggested.

If participants are enrolled in studies requiring use and/or storage of data and/or biological samples then separate consent will need to be obtained, and the data/samples managed and stored separately to REDUCE 2. No costs associated with these processes will be attributable to REDUCE 2.

* 1. Randomisation scheme

Patients will be randomised in a 1:1 ratio to receive the intervention of IPC insertion and talc administration or recurrent pleural aspiration.

* + 1. Method of implementing randomisation

Randomisation will occur at the baseline visit and will be carried out using the randomisation module in REDCap.

Minimisation is not being used due to low projected participant numbers.

Local site staff will access the trial database to reconfirm eligibility and perform randomisation which will be confirmed on screen.

Access to the registration and randomisation database will be available via the trial management team if required.

* 1. Blinding

This study is open-label as the differing nature of the interventions renders effective blinding impossible.

* 1. Baseline data

Once consented, trial participants will be seen by a member of the trial team who will undertake an initial assessment. The data will be entered on the relevant CRF.

Much of this information may already be available from recent consultations and will include:

* Demographics
* Relevant medical history
* Clinical assessment
* Observations
* Onset and nature of symptoms
* Pleural procedures to date
* Co-morbidities
* Medications
* NYHA classification
* Rockwood CFS
* Results of standard blood tests (these must have been drawn within 3 months prior to enrolment, unless more recent bloods are clinically indicated)
* NT-pro BNP
* Results of pleural fluid tests (most recent tests, no timeframe)
* PROMS
  + Visual-Analogue Scale (VAS) score to assess thoracic pain and breathlessness
  + Quality of life assessment using EQ-5D questionnaire
  + Assessment of the impact of heart failure on the participant’s life with the Minnesota Living with Heart Failure Questionnaire (MLHFQ)
* Imaging
  + PA chest x-ray (from within 2 weeks)
  + Thoracic ultrasound scan undertaken by a practitioner with at least Royal College of Radiologists Level 1 Thoracic Ultrasound competency
  + Echocardiogram including left ventricular ejection fraction and any other significant findings (from within 1 year)

Participants will then be randomised to either the IPC/talc arm or pleural aspiration arm. An appointment for either IPC insertion or pleural aspiration (day 0) should be made. This should be within four weeks of the baseline assessment. If an appointment cannot be made within this time, this should be recorded as a protocol deviation.

This visit is regarded as standard care.

* 1. Trial interventions, assessments and timeline
     1. IPC insertion or therapeutic pleural aspiration (Procedure - Day 0)

IPCs must be placed by an appropriately trained member of staff, but not necessarily a member of the trial team. The IPC inserted must be a BD PleurX provided by BD for the purposes of REDUCE 2. The IPC insertion CRF should be completed during or immediately after the procedure. Immediately following drain placement a therapeutic aspiration of the maximum clinically appropriate volume should be performed using the appropriate adaptor kit**.** This should ideally be done with the patient positioned so as to ensure the drain is in a dependent position.

As per usual clinical practice for IPC insertion a chest x-ray should be performed post-procedure to confirm adequate drain placement.

In the following 6 days the patients must have their IPCs drained daily. The drainage volume should be 1 litre, or the maximum clinically appropriate volume if less than 1 litre. The volume drained should be recorded in the trial booklet by the healthcare professional conducting the drainage. If local services cannot deliver this number of drainages, the minimum acceptable number is 4 in 6 days.

PleurX catheters and relevant consumables will be provided by BD. Please see TSP for full insertion details.

Participants in the recurrent aspiration arm will be undergo therapeutic pleural aspiration, with a maximum drainage volume of 1.5 litres, or the maximum clinically appropriate volume if less than 1.5 litres. The aspiration procedure is documented in the TSP. Participants will be issued with a specific participant trial booklet. Participants will then request further follow up as required for ad hoc drainages. These can also be arranged by healthcare professionals caring for these participants. The decision to undertake further therapeutic aspiration is to be taken by the treating physician in line with current practice – i.e. a combination of symptomology, clinical findings, oxygen requirement, radiological findings and any other relevant information. Due to clinical heterogeneity, exact criteria for aspiration are not specified here.

Prior to discharge, the participant will be issued with a participant trial booklet containing entry sheets for VAS scores and drainage volumes to be completed throughout the follow up period. This booklet will be specific to the IPC/talc arm.

Participants will be instructed to complete daily data entry sheets in their participant booklets from day 1 to day 14. These sheets will include VAS for chest pain and breathlessness, a record of analgesia use, a record of healthcare utilisations and a section for any other comments. The data sheets will also have a section for the volume of pleural fluid drained, to be completed contemporaneously by the healthcare professional who has undertaken drainage. The VAS should be completed within one hour of IPC drainage.

Participants will also be given an appointment diary which will outline the schedule for their follow-up period. This is contained within their data collection booklet. This should be completed with details of their next appointment at each consultation. All participants will be issued with a standard minimum amount of analgesia to take home to be taken as required, as outlined in the TSP.

This visit is regarded as standard care.

* + 1. Talc administration (1 week +/- 3 days) – IPC/talc arm only

Participants will attend their local trial centre 7 days (+/- 3 days) after IPC insertion. **Their catheter should be drained to dryness**, or as close to dryness as allowed by symptoms. Following this, they should undergo a chest x-ray (ideally PA) and have an appointment with a member of the trial team, who will perform a medical assessment as outlined on the appropriate CRF. VAS scores for chest pain and breathlessness will be recorded. The chest x-ray should be examined for evidence of lung entrapment and significant fluid. A thoracic ultrasound of the side where the IPC has been inserted should be performed, looking for evidence of fluid loculation and septation. An ultrasound CRF should be completed.

If there is evidence of **significant lung entrapment** (>25% of the hemi thorax without expanded lung visible on CXR as judged by two separate clinicians) or **significant pleural fluid** (pleural fluid, confirmed on thoracic ultrasound, occupying more than 25% of the hemi thorax as judged by two separate clinicians using visual estimation on chest x-ray), then the patient should be excluded from talc administration. These patients will remain under follow up on an intention to treat basis. Should there be disagreement regarding the degree of lung entrapment or fluid volume on chest x-ray, then a third independent clinician should be enlisted to provide a casting vote.

Participants may also not receive talc instillation for other clinical reasons not relating to the degree of lung entrapment or residual fluid. Such participants should have the details outlined on the appropriate CRF and may be discussed with the CI if needed.

Participants who do not meet the criteria for talc administration will continue to be followed up as per protocol.

**If a participant is eligible to proceed with talc instillation then this should be carried out on the same day where possible.**

If a participant is eligible for talc administration but is not deemed clinically appropriate due to eg a chest infection or the presence of surgical emphysema, talc administration (and all subsequent protocol stages) may be delayed by up to a week. This decision is at the discretion of the local trial team**.**

**Talc instillation must take place either on a Monday, Tuesday or Wednesday.** This is to ensure that participants’ IPCs are drained daily for at least 3 days following talc administration, reducing the risk of loculation formation.

The procedure for talc instillation is outlined in the appropriate Trial Specific Procedure (TSP).

**On the day following talc instillation the participant is required to attend for a clinical review, IPC drainage and for blood tests** including renal function and inflammatory markers. This is to mitigate for acute kidney injury secondary to fluid shifts and talc-related inflammatory response.

These visits are regarded as trial specific.

* + 1. Follow up blood tests

There is a theoretical risk of acute kidney injury related to fluid shifts secondary to IPC drainage in this cohort of patients who are already on high dose diuretics and potentially nephrotoxic medications. This risk is viewed to be maximal in the aggressive drainage phase, i.e. the two weeks following IPC insertion. During this phase renal function should be monitored twice weekly – on days 3, 7, 8 and 10. All bloods may be taken +/- 1 day from these dates however it is suggested that the blood test on day 7 be taken during the planned participant attendance before talc is administered. The blood tests on day 8 should be drawn during the planned post-talc review (see section above).

Blood tests on days 3 and 10 can be drawn at a location that is convenient to the participant that is felt to confer a low risk of COVID-19 exposure i.e. a community hospital or GP surgery if this has been previously agreed to.

Local study staff will review blood tests as they become available and action any results as required. Any deterioration in blood results will be recorded in the appropriate AE/SAE form. Appropriate clinical management will be determined by the local study site.

Blood tests will be taken in both arms at weeks 2, 4 and 12. The blood test schedule is shown below:

|  |  |  |
| --- | --- | --- |
| Study day | IPC arm | Therapeutic Aspiration arm |
| Baseline | *If not already done:*  FBC, U&E, Bone Profile, LDH, CRP, Clotting, NT pro-BNP | *If not already done:*  FBC, U&E, Bone Profile, LDH CRP, Clotting, NT pro-BNP |
| 3  1 day | FBC, U&E | - |
| 7  1 day | FBC, U&E | - |
| 8  1 day | FBC, U&E, CRP | - |
| 10  1 day | FBC, U&E, CRP | - |
| 14  3 day | FRC, U&E, Bone profile | FBC, U&E, Bone profile |
| 28  3 days | FBC, U&E, Bone profile | FBC, U&E, Bone profile |
| 84  1 week | FBC, U&E, Bone profile | FBC, U&E, Bone profile |

Blood test abbreviations:

FBC Full Blood Count

U&E Urea and electrolytes

Bone Profile *unabbreviated*

LDH Lactate Dehydrogenase

CRP C-reactive protein

NT pro-BNP N-terminal pro B-type natriuretic peptide

Clotting *unabbreviated*

* + 1. Community IPC Drainage

Following talc instillation all participants should receive fluid drainage in the community although if necessary, participants may attend their local trial centre. This will be undertaken by an appropriately trained healthcare professional throughout the follow-up period – in most cases this will be the local District Nurse team.

For the first week, the IPC should be drained daily, or a minimum of 5 times a week. Following talc administration, participants should have their IPCs drained daily (or at least 5 times per week) for the next two weeks. Drainage frequency will then reduce to (at least) 3 times weekly. After week 4 drainage frequency may reduce to twice weekly, however the frequency of drainage will be at the discretion of the patient and community team.

|  |  |  |  |
| --- | --- | --- | --- |
| Day | Week | Timepoint | Drainage Frequency |
| 0-21 | 0-3 | Procedure to week 3 | Daily or minimum of 5x weekly |
| 21-28 | 3-4 | Week 3 to 4 week FU visit | Minimum of 3x weekly |
| 28 onwards | 4 onwards | 4 week FU visit onwards | Minimum of 2x weekly |

Following drainage, the volume removed will need to be documented in participant booklet by the person removing the fluid. This will be in addition to any standard documentation which community nursing staff may be required to complete.

* + 1. Ad Hoc Therapeutic Pleural Aspirations

Participants in the therapeutic aspiration arm should contact the trial team for assessment if they feel they require a further therapeutic aspiration at any time. Wherever possible this should be arranged through the local trial team and the episode recorded in the appropriate CRF. The participant should be assessed clinically and a chest x-ray and thoracic ultrasound performed.

The decision to undertake further therapeutic aspiration is to be taken by the treating physician in line with current practice – i.e. a combination of symptomology, clinical findings, oxygen requirement, radiological findings and any other relevant information. Due to clinical heterogeneity, exact criteria for aspiration are not specified here.

If indicated, therapeutic aspiration should be carried out in line with the relevant SOP.

In the case of an emergency admission or the participant requiring aspiration in a location not served by the trial team the volume of fluid aspirated should be recorded in the participant’s trial booklet. The participant or their care team will be requested to contact the trial team to arrange a clinical review within one week of this event.

All visits and/or admissions for pleural intervention in the recurrent aspiration arm are regarded as standard care.

* + 1. Face-to-face appointments (Mandatory on week 2, 4, and 12) – both arms

The follow-up period for each patient is 12 weeks post procedure or until death, whichever is earlier.

During this time, clinical assessments will take place at weeks 2, 4 and 12 after IPC insertion/initial therapeutic aspiration. A remote consultation occurs at week 8 which may be face to face or via telephone/video-link. This may be carried out by any qualified member of the research team. All follow-up appointments should ideally take place in the participant’s base hospital or in an appropriate satellite centre. In the event that an assessment cannot be performed on the allocated day, the review appointments for week 2 and 4 can be rescheduled to occur 3 days before or after the protocol-stipulated day. For the week 8 and 12 reviews the window is 7 days before or after the stipulated date. If the participant cannot be assessed within these windows then another appointment should be made for as soon as possible, and the delay reported on a protocol deviation form.

Prior to assessment the participant’s IPC should be drained to dryness or as near tolerated by the patient. This drainage is to be carried out by trial staff on site. Participants in the control arm should be offered therapeutic pleural aspiration. The assessment should then be completed using the appropriate CRF and will include:

* Record of any contact with hospital services including hospital admissions and length of stay, outpatient care visit, emergency care visit, and ambulance service use
* Complications of pleural intervention
* Documentation of analgesia requirements
* PROMS
  + - Quality of life assessment using EQ-5D health questionnaire
    - Assessment of the impact of heart failure on the participant’s life with the Minnesota Living with Heart Failure Questionnaire (MLHFQ)
    - VAS for thoracic pain and breathlessness
* Volume and frequency of fluid drainage as recorded in patient’s drainage record book and any other pleural procedures
* NYHA class
* Rockwood CFS

During visits at weeks 2, 4 and 12 participants should have a chest x-ray (PA) and undergo thoracic ultrasound. An ultrasound CRF should be completed.

The clinical assessment must be carried out by a medical member of the trial team.

Completed pages from the participants’ booklets will be collected at each appointment.

The week 8 review will only involve the bullet pointed items above. If conducted remotely the PROMs will be sent to the participant via post or via an email link. The participant will be asked to complete and return them by post if they cannot complete electronically. Pre-paid addressed envelopes will be provided.

The visits at weeks 4 and 8 are considered to be study specific, non-standard care. The visits at weeks 2 and 12 are considered to be standard care. All investigations carried out at follow up visits are considered to be standard care.

**In light of the COVID-19 pandemic it is possible that participants and/or sites will judge that participant contact should be minimised. In recognition of this, follow up visits may be carried out remotely via telephone or video-link if sites are able to do this**. A protocol deviation form must be completed for each visit. Where possible chest x-rays should be undertaken in environments felt to confer a lower COVID-19 exposure risk such as community hospitals attached to trust sites. It is recognised that thoracic ultrasound will be very difficult to undertake in this manner however, therefore it is deemed non-essential.

* + 1. Chest x-rays

Participants will be asked to undergo a number of chest x-rays throughout the study, as mentioned in the sections above. For clarity, the number of expected x-rays is outlined below:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Therapeutic Aspiration arm | | | | |
| Event | Trial Specific | Standard Care | Data Capture | Comment |
| Screening/baseline |  | a |  | May not be required if participant has had CXR within last 2 weeks and repeat CXR not clinically indicated |
| 1st Aspiration (procedure) |  | a |  |  |
| 2 Week follow up | b |  |  |  |
| 4 Week follow up |  | a |  |  |
| 12 Week follow up |  | a |  |  |
| Minimum number of expected CXRs | | | | 5 |
| Maximum number of expected CXRs | | | | Governed by number of ad hoc aspirations required (Any ad hoc aspiration will require a pre- and post- procedure CXR, although if the effusion reaccumulation is identified as a result of a planned follow up CXR, only a post procedure CXR may be required) |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| IPC arm | | | | |
| Event | Trial Specific | Standard Care | Data Capture | Comment |
| Screening/baseline |  | a |  | May not be required if participant has had CXR within last 2 weeks and repeat CXR not clinically indicated |
| IPC insertion (procedure) | a |  |  | Post IPC insertion (standard care for IPC insertion) |
| Talc instillation | a |  |  | Pre talc instillation (standard care for talc instillation) |
| 2 Week follow up | b |  |  | For research purposes |
| 4 Week follow up |  | a |  |  |
| 12 Week follow up |  | a |  |  |
| Pleurodesis | a |  |  | Only required in case of pleurodesis (see section 7.7) therefore not all participants may need these CXRs. Standard care for IPC use |
| Post IPC removal | a |  |  |
| Minimum number of expected CXRs | | | | 6 |
| Maximum number of expected CXRs | | | | 8 |

a standard care for costings purposes

b trial specific for costings purposes

* 1. Pleurodesis

For the purposes of IPC removal, pleurodesis will be defined as the collection of less than, or equal to, 50mls of pleural fluid on three consecutive occasions, with chest opacification on the side of the IPC less than 25%, as judged by 2 independent clinicians. The x-ray must be taken after the third drainage of 50ml or less.

If a participant (or the district nursing team) feels their fluid volumes have dropped to these levels, they are encouraged to contact the local trial centre for assessment. The local trial team should then see the participant and assess them clinically and with a chest x-ray (see SOP). The appropriate CRF must be completed at this point. If pleurodesis is confirmed the IPC should be removed (see section 7.13).

Pleurodesis can be identified at any point throughout the study in the IPC/talc arm.

In the control arm, pleurodesis will be defined as chest x-ray opacification of less than 25%, with no further pleural interventions required throughout the duration of the study following the initial aspiration.

* 1. Data Collection Schedule

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Day** | **Event** | **Home or appointment** | **CRF or Participant Booklet** | **Comments** |
| / | Baseline/ Consent/ Randomisation | Appointment | CRF |  |
| 0 | IPC insertion/ Therapeutic aspiration | Appointment | CRF | Data collected both prior to and after IPC insertion or therapeutic aspiration |
| 1 |  | Home | Booklet |  |
| 2 |  | Home | Booklet |  |
| 3 |  | Home | Booklet | *Bloods for IPC arm* |
| 4 |  | Home | Booklet |  |
| 5 |  | Home | Booklet |  |
| 6 |  | Home | Booklet |  |
| 7 | Talc (IPC arm only) | Appointment | CRF | *Bloods* |
| 7 |  | Home | Booklet |  |
| 8 | Post talc review (IPC arm only) | Appointment | CRF | *Bloods* |
| 8 |  | Home | Booklet |  |
| 9 |  | Home | Booklet |  |
| 10 |  | Home | Booklet |  |
| 11 |  | Home | Booklet |  |
| 12 |  | Home | Booklet | *Bloods for IPC arm* |
| 13 |  | Home | Booklet |  |
| 14 (±3 days) | Outpatient Clinical Review | Appointment | CRF | Completed Participant Booklet pages collected  *Bloods for both arms* |
| 21 |  | Home | Booklet |  |
| 28 (±3 days) | Outpatient Clinical Review | Appointment | CRF | Completed Participant Booklet pages collected  Stamped addressed envelope for booklet return given  *Bloods for both arms* |
| 35 |  | Home | Booklet |  |
| 42 |  | Home | Booklet |  |
| 49 |  | Home | Booklet |  |
| 56 (±7 days) | Review | Variable | Booklet | **If face to face**, completed Participant Booklet pages collected.  **If telephone**, participant to post pages back using stamped addressed envelope |
| 63 |  |  | Booklet |  |
| 70 |  | Home | Booklet |  |
| 77 |  | Home | Booklet |  |
| 84 (±7 days) | Final Outpatient Clinical Review | Appointment | CRF | All remaining Participant Booklet pages collected  *Bloods for both arms* |
| ***END OF STUDY*** | | | | |
| Unspecified | Semi-structured Interview | Home | N/A | Interviews for 20 participants carried out via telephone |
| ***Drainage volumes to be recorded contemporaneously by healthcare professional who undertakes drainage*** | | | | |
| ***Ad hoc therapeutic aspirations are to be recorded in the relevant CRF, or in the participant booklet if not carried out in the trial centre*** | | | | |
| ***All VAS scores to be taken within 1 hour of IPC drainage if applicable, or otherwise at 12.00*** | | | | |

* 1. Qualitative assessments

An important part of a feasibility study is to record and assess participants’ experiences of the trial processes, interventions and follow up. A selection of patients deemed eligible to participate in REDUCE 2 will be invited to semi-structured interviews – both patients who accepted randomisation and those that did not will be invited.

All interviews will be digitally audio recorded, transcribed verbatim by an approved third party provider and anonymised prior to being uploaded to data management software for analysis.

* + 1. Patient interviews

Information about the optional interviews will be included in the main Participant Information Sheet. Information regarding consent for interviews is contained in section 7.2. Patients who elect not to enter the trial will also be offered the opportunity to participate in the interview process (information about both the main trial and the optional interviews is included in the same Participant Information Sheet) and consented if they agree to do so.

Interviews will be carried out within the follow up period. Participants will be contacted to arrange an interview at a suitable time for them. Participants will be remined to review PIS B prior to interview and, if required, can be sent a new copy via email or post. Interviews will be carried out via telephone and the interview will be audio recorded. Consent will be reaffirmed prior to interview commencement. Interviews will be carried out by an appropriate member of the coordinating central trial team.

The topics covered will include:

* The participant experience of refractory pleural effusion secondary to heart failure
* The participant experience of IPC insertion (if applicable)
* The participant experience of regular IPC drainage in their home environment (if applicable)
* The participant experience of talc instillation (if applicable)
* The participant experience of recurrent therapeutic pleural aspirations
* Whether the participant feels the pleural intervention(s) have made a positive impact on their life
* Would the participant recommend the care to another patient in a similar condition to themselves
* Suggested improvements to study processes, documents or other technical aspects
* Reasons for declining participation (if applicable)

A sample size of 20 participants is envisaged to be sufficient for the purposes of this study. This sample will include participants from both arms and those that declined to participate in the study. However the final number of participants interviewed will be determined by the number required to achieve data saturation.

* 1. Withdrawal criteria

Trial participants have the right to withdraw from the trial at any point. Withdrawal does not have to be justified and will not affect future or on-going care. In the event of withdrawal, any details available for the reason(s) should be recorded in the participant’s CRF, and clarification on the nature of the withdrawal of consent, as outlined below, should be sought. Participants may still be stratified as ‘alive’ or ‘dead’ at the end of their follow-up period, unless consent for clinical data use is withdrawn. Participants who withdraw before randomisation will not be included in the final analysis.

Withdrawal of consent to all trial involvement

The participant withdraws all consent for trial involvement, including sample storage and analysis, and for any data already collected to be used in analyses. Samples already taken and follow-up data should be destroyed as per local policy.

Withdrawal of consent to follow-up and further clinical data collection only

The participant withdraws consent to further follow-up visits and recording of clinical data.

They maintain consent for blood and fluid samples already taken to be analysed, and for clinical data already collected to be used in analyses.

Withdrawal of consent to follow-up, further clinical data collection, and clinical data use

The participant withdraws consent to further follow-up visits, recording of clinical data, and the use of any clinical data already collected in analyses.

* 1. Storage and analysis of clinical samples

Standard blood tests are required to be taken during the study. Blood drawing technique and equipment should be as per local protocol. No long term sample storage is required.

Pleural fluid samples are to be taken prior to enrolment, again to be processed locally. These are to include protein, LDH, glucose, cytology and MC&S. Sampling equipment and technique should be as per local protocol. These samples are not required to be stored by this protocol.

All of the above are regarded as standard care.

* 1. Removal of IPCs

Once inserted, IPCs may be removed at any time at the clinical discretion of the patient’s primary physician, at the request of the patient, or at the discretion of the trial team. Common reasons for IPC removal will be outlined on follow-up CRFs. Potential reasons include (but are not limited to):

|  |  |
| --- | --- |
| Reason for removal | Complete AE form |
| Local subcutaneous or pleural infection |  |
| Intolerable pain |  |
| Significant fluid loculation |  |
| IPC failure due to intractable blockage, fracture or other means |  |
| Cessation of fluid drainage due to pleurodesis |  |

In the case of cessation of pleural fluid drainage, the criteria for pleurodesis must have been met (please see section 6.7). For all other reasons, an AE form should be completed as these are considered adverse events.

If a drain is to be removed, patients should be given an appointment to have this done within 14 days of the clinical assessment at which this decision was taken. Removal of indwelling pleural catheters should be performed by trained staff under aseptic conditions and should be followed by a chest x-ray. The procedure should be recorded on the relevant CRF.

Any patient who has their IPC removed during their trial period will continue to undergo planned follow-up for the full trial period.

* 1. Blockage of IPCs

All care should be taken to ensure IPCs do not become blocked, beginning with an adequate flush at the end of sclerosant administration. If there is a suspicion that blockage has occurred, indicated by cessation of drainage with persistent chest x-ray or ultrasound changes, standard local unblocking procedures should be followed. This may involve a short hospital admission for administration of intrapleural urokinase or similar. Such events should be documented on the appropriate CRF, on an adverse event form (or SAE form if appropriate) and, as per normal, in the patient’s notes. An SOP for a suggested drain unblocking protocol will be provided.

* 1. IPC Infections

Suspected IPC infections should be assessed and managed in line with standard care and a relevant AE form completed. Suggested management includes:

* Clinical assessment
* Blood tests
* CXR
* Blood and pleural fluid cultures
* Skin/wound swabs (if possible entry site/subcutaneous infection)
* Relevant antibiotics guided by local protocols and culture results
* IPC removal can be considered if clinically indicated

Where possible, suspected or confirmed infections should be discussed with the central study team prior to proceeding to IPC removal.

* 1. End of trial

The trial ends at the completion of 12 week follow up for the last-recruited participant or the final participant interview, whichever is later. At the end of each patient’s follow-up period they will be stratified as ‘alive’ or ‘dead,’ and survival data collated. Further information regarding participants’ health status and survival may be obtained by accessing the NHS central register.

Those who still have an indwelling pleural catheter in situ will have their care devolved to the appropriate local services at 12 weeks.

1. TRIAL TREATMENTS
   1. Name and description of investigational medicinal product(s)

None

* 1. Name and description of each Non-Investigational Medicinal Product (NIMP)

In addition to talc slurry, intrapleural lignocaine is stipulated in the protocol. Analgesia such as paracetamol and morphine may also be given at the discretion of the local trial team.

* + 1. Talc slurry

Medicinal sterile talc as used in this trial is mined in Luzenac, France. It is marketed in the UK as Steritalc® (Novatech) and imported by GB UK Healthcare Ltd. Talc is a naturally occurring mineral which, when processed for medical use, takes the form of a white powder of controlled particle size (mean particle size 25 µm). It is not licensed in the UK but is commonly used for the induction of pleurodesis, usually to prevent recurrence of malignant pleural effusions or pneumothoraces. Medicinal, ungraded talc has been licensed in the USA since 2003. Prior to introduction into the pleural cavity it is reconstituted into slurry using an inert solvent such as 0.9% saline. The typical dose of talc is 2-4 grams. Common side effects following pleural administration of talc are mild pleuritic pain and low-grade fever.

For the purposes of this trial, the intervention arm of the study will receive a talc slurry instillation seven days (+/- 1 day) after IPC insertion, via the IPC. The slurry will consist of 4 grams of talc mixed with 50 mls of 0.9% saline.

Regulatory status of the drug

The MHRA has confirmed that because talc is being used in this study as part of a comparison of techniques rather than evaluating a specific product, this trial is not a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC

Although it is commonly used for pleurodesis in the UK, Steritalc does not have marketing authorisation for the purpose.

The manufacturer is Novatec SA, La Ciotat, France.

The UK importer is GBUK Group Limited, Woodland House, Blackwood Hall Business Park, North Duffield Selby, North Yorkshire, YO8 5DD.

Product Characteristics

See separate Summary of Product Characteristics for Steritalc.

Drug storage and supply

Steritalc is available to all UK hospitals via their normal supply and procurement channels. No specialist ordering, storage or processing procedures are required. Participating sites are requested to source Steritalc locally from their own procurement channels. Unused supply can be used in non-trial patients in an unrestricted manner.

Study medication will be stored and dispensed by the trial site’s pharmacy department in accordance with Good Clinical Practice, Good Manufacturing Practice and pharmacy department SOPs. Delivery of Steritalc should be carried out according the TSP.

Normal saline is a standard medical product available in all UK hospitals. No specialist ordering, storage or processing procedures are required. Participating sites are requested to source normal saline locally from their own procurement channels. Unused supply can be used in non-trial patients in an unrestricted manner.

Brexit

The UK distributor of Steritalc, GBUK Group Limited, have provided assurances that the UK supply of Steritalc is secure and that robust procedures are in place to ensure security of supply to UK hospitals in the post-Brexit period.

Preparation and labelling of Medicinal Product

The procedure for preparation and labelling of talc is fully described in the relevant TSP. Briefly, 4 grams of Steritalc should be mixed with 50 mls of normal saline and a slurry formed. This slurry is prepared under sterile conditions.

Dosage schedules

Talc is to be given only once in this study, at day 7.

The route of administration is intrapleural, via an IPC. Relevant giving sets will be supplied with to trial sites along with the trial set up equipment provided by BD.

Full details of administration are contained within the relevant TSP.

Dosage modifications

The doses of talc is non-modifiable – all participants will receive standard doses. There is no adjustment for factors such as weight or renal function.

Known drug reactions and interaction with other therapies

No interactions are known with intrapleural talc or intrapleural saline.

Concomitant medication

This protocol places no restriction on concomitant medications. However any should be clearly recorded in the relevant CRF.

Trial participants should not undergo thoracic surgery or radiotherapy during the trial period.

Trial restrictions

This protocol places no specific restrictions on dietary intake for participants although it is anticipated that many will already have restricted fluid intakes from their pre-existing management plans.

Co-enrolment in concurrent trials is not explicitly prohibited but should be discussed with the central trial team prior to enrolment.

Pregnancy or planned pregnancy is an exclusion criterion from this trial. Female participants are not expected to be of childbearing age (the mean age of female participants in REDUCE was 79, range 60-91). Contraception should therefore be used for sexually active female participants for the duration of the trial.

Assessment of compliance with treatment

As talc will be given only once and administered by a member of the trial team, no issues with compliance are anticipated.

* + 1. Intrapleural lidocaine

All trial participants who undergo talc instillation will have a 3mg/kg dose of Lidocaine 1% w/v solution for injection administered intrapleurally prior to receiving talc slurry.

Lidocaine has UK market authorisation for infiltration anaesthesia, intravenous regional anaesthesia and nerve blocks.

The 1% lidocaine to be used is of standard preparation. Lidocaine is available to all UK hospitals via their normal supply and procurement channels. No specialist ordering, storage or processing procedures are required. Participating sites are requested to source lignocaine locally from their own procurement channels. Unused supply may be used in non-trial patients in an unrestricted manner.

Delivery of lidocaine should be carried out according the TSP.

* + 1. Analgesia

Appropriate analgesia is to be given at the discretion of the local trial team. This may include paracetamol and a clinically appropriate opiate preparation such as oramorph or oxynorm.

1. SAFETY REPORTING
   1. Definitions

|  |  |
| --- | --- |
| **Term** | **Definition** |
| **Adverse Event (AE)** | Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product, medical device or intervention and which does not necessarily have a causal relationship with this treatment.  An AE can be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the research procedure, whether or not considered related. AEs require continuous assessment. |
| **Adverse Reaction (AR)** | The distinguishing feature between an AR and AE is whether there is evidence to suggest there is a causal relationship between the event and the research procedure. |
| **Serious Adverse Event (SAE)** | “Any untoward medical occurrence that:   * Results in death; * Is life-threatening;\* * Requires hospitalisation or prolongation of existing hospitalisation; * Results in persistent or significant disability or incapacity; or * Consists of a congenital abnormality or birth defect.”   \* Life-threatening refers to an event where the subject was at risk of death at the time of the event; not to an event that hypothetically might have caused death if it was more severe. Medical judgement should be exercised in deciding whether an SAE/SAR is serious in other situations. Those events that are not immediately life-threatening or do not result in death or hospitalisation, but may jeopardise the subject or may require intervention to prevent one or more of the other outcomes listed, should be considered serious. |
| **Serious Adverse Reaction (SAR)** | Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure. |
| **Suspected Unexpected Serious Adverse Reaction (SUSAR)** | Any SAE that is classed in nature as serious and there is evidence to suggest there is a causal relationship between the event and the research procedure, but where that event is unexpected. |
| **Accidents Incidents or near Misses (AIMS)** | The AIMS system is common in many NHS Trusts and implements and NHS Trust’s policy on Incident Reporting – including relevant AEs that occur in relation to research and during normal clinical practice. |
| **Summary of Product Characteristics (SmPC)** | The SmPC is a technical document which profiles a drug and contains information relating to composition, form and strength, known reactions, cautions, shelf-life and storage conditions. |
| **CAUSALITY** | The relationship of each adverse event to the trial procedure must be determined by a medically qualified individual according to the following definitions:  **NOT RELATED** Temporal relationship of the onset of the AE, relative to the administration of the product, is not reasonable or another cause can explain the occurrence  **UNLIKELY** Temporal relationship of the onset of the AE, relative to the administration of the product, is likely to have another cause which can by itself explain the occurrence  **POSSIBLY RELATED**\* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause  **PROBABLY RELATED**\* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and the event is more likely to be explained by the product than any other cause  **DEFINITELY RELATED**\* Temporal relationship of the onset of the event, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive  \* Where an event is assessed as possibly, probably or definitely related, the event is an adverse reaction |
| **EXPECTEDNESS** | Adverse reactions must be considered as unexpected if they add significant information on the specificity or severity of an expected adverse reaction. The expectedness of an adverse reaction shall be determined according to the information defined in the study protocol.  **EXPECTED** Reaction previously identified and described in protocol.  **UNEXPECTED** Reaction not previously described in the protocol. |
| **INTENSITY** | **MILD** An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities  **MODERATE** An event that is sufficiently discomforting to interfere with normal everyday activities  **SEVERE** An event that prevents normal everyday activities |

* 1. Operational definitions for (S)AEs

The population of patients involved in REDUCE 2 is one in which a high number of adverse events are expected. Many of these will be a direct consequence of the patient’s underlying disease (which is an entry criteria). Other events may occur as a result of a trial-related intervention but are well-documented and regarded as normal complications of the administration of talc or use of an IPC.

The assignment of causality to an adverse event should be made by the investigator responsible for the care of the participant based on the definitions above (see 9.1). If any doubt about causality exists, the local investigator should inform the Trial Manager or Chief Investigator.

Anticipated adverse events (if the event is not listed here it would be classed as ‘unexpected’)

Anticipated adverse events in this setting are listed below. All are well documented as known to be caused by the underlying disease, the clinical procedure or talc.

***Heart Failure***

* Hospital admission due to exacerbation of heart failure (e.g. for intravenous diuretics) or for titration of medications (e.g. acute kidney injury secondary to diuretics)
* Death due to heart failure or other cardiac pathology

***Use of an IPC***

* Known immediate complications of IPC insertion including:
  + Bruising
  + Discomfort around IPC site
  + Bleeding associated with IPC insertion
  + Thoracic injury or organ damage related to IPC insertion
  + Leakage of pleural fluid around the IPC
  + Intrapleural infection related to IPC insertion
  + Subcutaneous infection at IPC site
  + IPC becoming dislodged or falling out
* Medium to long term complications including:
  + Pleural or subcutaneous infection
  + Development of septations or loculations in the pleural effusion
  + IPC blockage
  + IPC failure requiring replacement.

***Therapeutic Pleural Aspiration***

* Known immediate complications of pleural aspiration including:
  + Bruising around aspiration site
  + Discomfort at aspiration site
  + Bleeding associated with aspiration
  + Thoracic injury or organ damage related to aspiration
  + Subcutaneous or pleural infection related to aspiration
  + Pneumothorax
* Medium to long term complications including:
  + Pleural or subcutaneous infection
  + Development of septations or loculations in the pleural effusion

***Talc Slurry***

Safety Information is a combination of the SmPC, current literature and clinical experience. These events would not be considered to be SUSARs unless the severity of the event was considered to be unexpected. These events would be recorded and reported as (S)ARs.

* Fever after administration (≤39°C) of talc
* Chest pain after administration of talc requiring analgesia
* Mild tachycardia after administration (≤20 beats per minute over baseline) of talc
* Dysrhythmia
* Hypotension/hypovolaemia
* Tachypnoea after administration of talc (increase in respiratory rate of ≥4 breaths per minute over baseline)
* New hypoxia after administration of talc (to saturation of ≥92% on air, not requiring supplemental oxygen)
* Pulmonary oedema
* Pneumonia
* Known medium term complications including pain and failure of pleurodesis which may require further intervention.

The SmPC for Steritalc also lists more severe potential complications as listed below. The TSC are satisfied that the risk of these complication is extremely low, evidenced by widespread clinical practice. These events would be recorded and reported as SARs.

* myocardial infarction
* pneumonitis
* acute reparatory distress syndrome

If there are any updates made to the SmPC or current literature, these will be reviewed by the Chief Investigator and Sponsor and a joint decision made whether the updated information will be added to the list of Anticipated Events listed in the protocol.

* 1. Recording and reporting of (S)AE(s) – see Safety Reporting flow chart in Appendix

All Adverse Events will be recorded in the participant’s medical notes and AE recording log CRF. The AE log will be reviewed by a clinician with delegated responsibility for Safety Reporting assessment and uploaded to the database within one week of the event.

* + 1. Recording and reporting of SAE(s)

Events that meet the criteria for being assessed as ‘serious’ will only be reported to the Sponsor on the NBT SAE/SAR/SUSAR Initial Report Form if they are also possibly, probably or definitely related to the trial procedures (form to be completed electronically in REDCap). Events that have been classed as possibly, probably or definitely related to the trial procedures will also be rated against the anticipated events for expectedness to determine if the event is a SUSAR. Events that are assessed as serious but unrelated to the trial procedures will be recorded on the AE log and uploaded to the database within one week.

SAEs will be reported to the Sponsor within 24 hours as described in the NBT SOP for Safety Reporting ([https://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures).](https://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures)%20%20but%20electronically%20via%20REDCap) The form will be completed electronically in REDCap, where a completed form can be saved as a PDF and emailed to researchsponsor@nbt.nhs.uk. The Sponsor will perform an initial check of the report and request any additional information.

In the event of an ongoing event, any change of condition or other follow-up information should be uploaded to the Adverse Event outcome section of the database. The completed form should be emailed to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

See <https://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures> for current Safety Reporting SOP and reporting forms. These forms are to be completed in REDCap.

All SAEs assigned by the PI or delegate (or following central review) as both suspected to be related to trial procedures and unexpected will be classified as **SUSARs** and will be subject to expedited reporting to the main REC which granted approval for the study. The Chief Investigator will inform the REC within 15 days of the occurrence.

Any questions concerning adverse event reporting should be directed to the trial coordination centre in the first instance.

* + 1. Outcome grading of adverse events

Adverse events are graded as either: resolved, stabilised, on-going, resolved with sequelae or death.

* + 1. Timeframes for recording and reporting of SAEs, SARs AND SUSARs

Reporting of adverse events starts at the following timepoints:

* For AEs / SAEs – consent
* For ARs / SARs and SUSARs – consent

Reporting of adverse events will cease after completion of the 12 week follow up period. As the administration of talc is a single intervention and the IPC insertion and daily drainage regimen all occur in the first two weeks, the likelihood of adverse events occurring beyond the planned follow up period is considered to be low.

* 1. Responsibilities

Principal Investigator (PI):

Checking for AEs and ARs when participants attend for treatment / follow-up.

1. Using medical judgement in assigning seriousness, causality and whether the event/reaction was anticipated using the Anticipated Event Information provided in the protocol about expected adverse events specific to this patient population.
2. Ensuring that all SAEs are recorded and reported to the sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available. Ensuring that SAEs are chased with Sponsor if a record of receipt is not received within 2 working days of initial reporting.
3. Ensuring that all other AEs and ARs are recorded on the AE log and uploaded to the database within one week.

Chief Investigator (CI) / delegate or independent clinical reviewer:

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated (in line with the Anticipated Event Information) where it has not been possible to obtain local medical assessment.
3. Using medical judgement in assigning whether an event/reaction was anticipated or expected in line with the Anticipated Event Information provided in the protocol about expected adverse events specific to this patient population.
4. Immediate review of all SUSARs.
5. Review of specific SAEs and SARs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.

Sponsor: (NB where relevant these can be delegated to CI)

1. Central data collection and verification of AEs, ARs, SAEs, SARs and SUSARs according to the trial protocol onto a database.
2. Reporting safety information to the CI, delegate or independent clinical reviewer for the ongoing assessment of the risk / benefit according to the Trial Monitoring Plan.
3. Reporting safety information to the independent oversight committees identified for the trial (Trial Steering Committee (TSC)) according to the Trial Monitoring Plan.
4. Expedited reporting of SUSARs to REC within required timelines.
5. Notifying Investigators of SUSARs that occur within the trial.

Trial Management Group (TMG):

The TMG will review all (S)AEs monthly.

Trial Steering Committee (TSC)/ Data Monitoring Committee (DMC):

In accordance with the TSC Charter, periodically reviewing overall safety data to determine patterns and trends of events, or to identify safety issues, which would not be apparent on an individual case basis.

* 1. Notification of deaths

Due to the co-morbidities of patients participating in REDUCE 2 only deaths deemed related to the trial procedures or if they occur earlier than expected will be reported to the sponsor as SAEs (until the end of the 12 week follow up period). Deaths in line with disease progression and deemed unrelated to the trial procedures will be recorded on the Adverse Event log and uploaded to the database within one week.

* 1. Pregnancy reporting

It is not anticipated that the REDUCE 2 patient cohort will result in any pregnancies. Any pregnancies that occur during the 12 week follow up period should be reported to the sponsor.

* 1. Overdose

The likelihood of an overdose is considered very low as the single dose of talc will be administered by healthcare professionals.

An overdose is considered to constitute any talc administration over 4 grams.

Any overdose should be reported as a protocol deviation and if appropriate, an SAE form should be completed concurrently.

Overdosed patients will not be removed from final analysis.

* 1. Reporting urgent safety measures

If any urgent safety measures are taken the CI/Sponsor shall immediately and in any event no later than 3 days from the date the measures are taken, give written notice to the relevant REC of the measures taken and the circumstances giving rise to those measures.

* 1. The type and duration of the follow-up of participants after adverse reactions.

Patients who experience adverse reactions to any research procedure will be followed up in line with the 12 week trial follow up period. Extended follow up is not stipulated by this protocol.

Any SUSAR will need to be reported to the Sponsor irrespective of how long after trial procedures the reaction has occurred until resolved.

1. STATISTICS AND DATA ANALYSIS
   1. Sample size calculation

The proposed study has a primary aim of investigating feasibility to recruit n = 40 in preparation for a definitive study (tentatively named REDUCE 3). The study is a feasibility study and a formal power calculation is not warranted as such. However, a justification for sample size by other means is required.

It is generally considered not unreasonable for feasibility studies and pilot studies to have a sample size equal to approximately 10% to 20% of the sample size that would be needed in a definitive trial. Based on REDUCE, an estimated sample sizes for a definitive trial REDUCE 3, would be in the region of 140 in total. However, an inflation of this number is warranted given the multi-site nature of the study.

Data from this study, combined with extant literature and findings from REDUCE, will be used to inform power calculations for a definitive study. These calculations will balance inadvertent under estimation or inadvertent overestimation of sample size. Setting the feasibility target to be higher than cited rules will refine this balance. Using the sample size procedure by Browne [35], if N = 40 is recruited, the estimated sample size will, on average, have increased precision with an average reduction in error estimate of 33%. Increasing sample size beyond N = 40 will have marginal benefit on overall accuracy.

In order to demonstrate feasibility, the absolute number recruited would need to be at least 80% of target (i.e. recruit at least 32 within the specified timeframe) and if >= 50% eligible patients are successfully randomised.

* 1. Statistical analysis plan

The study is a feasibility study concerned with recruitment and as such recruitment rates, retention rates and data completion will be recorded, summarised and interpreted by study duration, by randomised arm and site.

Secondary outcomes will be summarised between arms using standard descriptive statistics.  Outcome measures will be compared between arms on an ITT basis using well established and appropriate standard statistical techniques for comparing two independent groups.  The approaches include:

* Chi-square permutation test for binary outcomes (successful pleurodesis at 5 and 14 weeks; all-cause mortality) with effect size estimated using the Mantel-Haenszel odds ratio and its estimated 95% confidence interval.
* Two group independent samples t-test including 95% confidence interval for effect and standardised effect for scale level data (VAS for breathlessness, VAS for pain, Quality of Life, Minnesota Living with Heart Failure)
* Two group non-parametric assessment (Mann Whitney Wilcoxon test, and Hodges Lehman Estimator) for between groups differences in count and skewed data (number of pleural aspirations, total volume aspirated, loculated pleural fluid, Rockwood Clinical Frailty Score)
* Chi-square test of linear association (NYHA Heart Failure Classification)
* Kaplan-Meier estimates and the Cox-Mantel log-rank test for time to event and censored data (all-cause mortality)
* Description and interpretation of Adverse Events by randomised arm.

A comprehensive Statistical Analysis Plan will be written for scrutiny by the TSC.

1. DATA MANAGEMENT

**See separate DMP**

The majority of data will be captured electronically using the REDCap system. This will ensure that data captured comply with the GCP standards that trial data should be:

* Accurate
* Legible
* Contemporaneous
* Original
* Attributable
* Complete
* Consistent
* Enduring
* Available when needed
  1. Archiving

Study documents (paper and electronic) will be retained in a secure location during and after the trial has finished. All essential documents, including patient records and other source documents will be retained in accordance with North Bristol NHS Trust’s Archiving SOP following the end of a study. Where electronic records are in use, Trust policy will be followed.

1. MONITORING, AUDIT & INSPECTION

The study will be monitored in accordance with North Bristol NHS Trust’s Monitoring SOP. All trial related documents will be made available on request for monitoring and audit by North Bristol NHS Trust, the HRA and for inspection by the Medicines and Healthcare products Regulatory Authority or other licensed bodies. The monitoring plan will be developed and agreed by the sponsor.

1. ETHICAL AND REGULATORY CONSIDERATIONS
   1. Research Ethics Committee (REC) review & reports

* before the start of the trial, approval will be sought from a REC for the trial protocol, informed consent forms and other relevant documents e.g. advertisements and GP information letters
* substantial amendments that require review by REC will not be implemented until the REC grants a favourable opinion for the trial (note that amendments may also need to be reviewed and accepted by the MHRA and/or NHS R&D departments before they can be implemented in practice at sites)
* all correspondence with the REC will be retained in the Trial Master File/Investigator Site File
* an annual progress report (APR) will be submitted to the REC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the trial is declared ended
* it is the Chief Investigator’s responsibility to produce the annual reports as required.
* the Chief Investigator will notify the REC of the end of the trial
* if the trial is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination
* within one year after the end of the trial, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC
  1. Peer review

The study has undergone extensive internal and external peer review throughout its’ design process. Peer reviewers are of broad expertise and experience appropriate to the scale of the study.

* 1. Public and Patient Involvement

Patients with experiences of persistent pleural effusions, IPCs and/or talc pleurodesis were involved in the PPI process. They have provided insight and guidance on:

* Design of the study
* Management of the study
* Undertaking the study
* Analysis of results
* Dissemination of findings

Their responses and suggestions have been incorporated into the study protocol and patient facing documentation.

A patient with persistent pleural effusion is a member of the TSC.

* 1. Regulatory Compliance

REDUCE 2 will not commence until a favourable REC opinion is obtained.

The protocol and trial conduct will comply with the Medicines for Human Use (Clinical Trials) Regulations 2004 and any relevant amendments.

* + 1. Ionising radiation

This protocol stipulates the use of ionising radiation in the form of chest x-rays. These will be carried out in line with the Ionising Radiation (Medical Exposure) Regulations.

The use of chest x-rays is justified by their clinical importance in assessing pleural effusions and use in standard care of patients with refractory cardiogenic pleural effusions.

The frequency of chest x-ray use in this protocol may be higher than in standard care at some sites. The deviation from standard care is justified as it will allow for more accurate delineation of the time course of changes within the pleural space following talc instillation. The radiation burden that these extra films will confer is not felt to be significant in the patient population that is being sampled.

Their use in this protocol has been assessed by a Medical Physics Expert and a Clinical Radiation Expert.

* 1. Protocol compliance

Prospective planned deviations or waivers to this protocol are not allowed under the UK regulations on Clinical Trials and must not be used e.g. it is not acceptable to enrol a participant if they do not meet the eligibility criteria or restrictions specified in the trial protocol.

Accidental protocol deviations can happen at any time. They must be adequately documented in the deviation log on REDCap and reported to the Chief Investigator and Sponsor immediately.

See R&I SOP RI/QMS/SOP/012 and associated reporting forms available at<https://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures>. These forms are to be completed in REDCap where the completed form can be saved and emailed to researchsponsor@nbt.nhs.uk.

Deviations from the protocol which are found to frequently recur are not acceptable, will require immediate action and could potentially be classified as a serious breach.

* 1. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree:

* the safety or physical or mental integrity of the participants of the trial; or
* the scientific value of the trial

In case of a serious breach:

1. the sponsor will be notified immediately of any case where the above definition applies during the trial conduct phase
2. the sponsor of a clinical trial will notify the licensing authority in writing of any serious breach of
   1. the conditions and principles of GCP in connection with that trial; or
   2. the protocol relating to that trial, as amended from time to time, within 7 days of becoming aware of that breach
   3. Data protection and patient confidentiality

All investigators and trial site staff must comply with the requirements of the Data Protection Act 2018 with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act’s core principles.

The database and randomisation system will be designed so as to protect patient information in line with (i) the Data Protection Act 1998 until 24 May 2018, and (ii) the General Data Protection Regulation, as from time to time amended from 25 May 2018. Trial staff will ensure that the participants’ anonymity is maintained through protective and secure handling and storage of patient information at the trial centres (as relevant). All documents will be stored securely and only accessible by trial staff and authorised personnel. Data will be collected and retained in accordance with the relevant data protection legislation.

Further information can be found in the Data Management Plan.

* 1. Financial and other competing interests for the chief investigator, PIs at each site and committee members for the overall trial management

Chief Investigator and committee members have signed a TSC Charter declaring conflicts of interest.

* 1. Indemnity

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no.2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm.

* 1. Amendments

**See R&I SOP** RI/QMS/SOP/003 ‘Research Study Amendments’available athttps://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures

* 1. Post trial care

After week 12, patient care will be fully devolved to local services. Participants who still have IPCs in situ will continue to be drained at the clinically determined frequency. Participants whose IPCs have been removed will be managed as clinically indicated.

BD will continue to provide IPC related consumables for participants beyond the trial period until no longer required.

Participants in the therapeutic aspiration arm may be offered IPC insertion +/- talc once they have completed the follow up period.

* 1. Access to the final trial dataset

See separate DMP

1. DISSEMINATION POLICY
   1. Dissemination policy

Once submitted to the database, the study data is the property of North Bristol NHS Trust.

Locally completed documents in collaborating sites may remain on site in appropriate storage.

On trial completion data analysis will occur and trial report compiled. This will be published in an open access journal and made available to all sites and surviving participants unless they state otherwise. Additionally a participant-friendly study outcome document will be produced for participants who wish to receive it.

The final trial report and presentations associated with it will be submitted to BD and Sponsor prior to publication and/or presentation.

The study protocol and statistical analysis plan will be published in an open access journal.

* 1. Authorship eligibility guidelines and any intended use of professional writers

Authorship will be in line with the International Committee of Medical Journal Editors guidelines.

1. APPENDICES
   1. Appendix 1-Risk (full risk assessment available on request)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Risks associated with trial interventions**  A ≡ Comparable to the risk of standard medical care  B ≡ Somewhat higher than the risk of standard medical care  C ≡ Markedly higher than the risk of standard medical care | | | | |
| All risks entailed in REDUCE 2 are categorized as grade A. This is due to the fact that all interventions are already established standard medical care in similar patient cohorts. | | | | |
| **Key risks associated with planned therapeutic interventions** | | **Plan to minimise risk** | | |
| **Intervention** | **Body system/ Hazard** | **Activity** | **Frequency** | **Comments** |
| **IPC insertion** | Thorax: Pain | Appropriate local anaesthesia +/- sedation, appropriate analgesia | Once | See TSP |
| **IPC insertion** | Thorax: Infection | Sterile technique, appropriate antibiotics if required | Once | See TSP |
| **IPC insertion** | Thorax: Local organ injury | Correct use of ultrasound to guide procedure | Once | See TSP |
| **IPC insertion** | Thorax: Bleeding | Checking of coagulation studies and platelets, Correct use of ultrasound to guide procedure | Once | See TSP |
| **IPC insertion** | Thorax: Procedure Failure |  | Throughout trial | See TSP |
| **Talc pleurodesis** | Systemic talc embolization | Use of correctly graded talc | Once | Steritalc is graded to avoid talc embolisation |
| **Talc pleurodesis** | Pain | Use of appropriate intrapleural anaesthesia and systemic analagesia | During and post talc instillation | See TSP |
| **Talc pleurodesis** | Fever | Use of paracetamol as required | Once |  |
| **Talc pleurodesis** | Infection | Sterile instillation technique, appropriate antibiotics if required | Once | See TSP |
| **Talc pleurodesis** | Cardiovascular compromise | Clinical assessment before and after procedure, appropriate clinical management as required | Once | See TSP |
| **Talc pleurodesis** | Respiratory compromise | Clinical assessment before and after procedure, appropriate clinical management as required | Once | See TSP |
| **IPC drainage** | Infection | Sterile technique, appropriate antibiotics if required | Throughout trial | See TSP |
| **IPC drainage** | IPC blockage | IPC care in line with TSP, flushing as required | Throughout trial | See TSP |
| **IPC drainage** | IPC displacement / failure / fracture | IPC care in line with TSP | Throughout trial | See TSP |
| **Therapeutic Aspiration** | Thorax: Pain | Appropriate local anaesthesia +/- sedation, appropriate analgesia | Throughout trial | See TSP |
| **Therapeutic Aspiration** | Thorax: Infection | Sterile technique, appropriate antibiotics if required | Throughout trial | See TSP |
| **Therapeutic Aspiration** | Thorax: Local organ injury | Correct use of ultrasound to guide procedure | Throughout trial | See TSP |
| **Therapeutic Aspiration** | Thorax: Bleeding | Checking of coagulation studies and platelets, Correct use of ultrasound to guide procedure | Throughout trial | See TSP |
| **Therapeutic Aspiration** | Thorax: Procedure Failure |  | Throughout trial | See TSP |
| Risk mitigation processes:   * This protocol has been peer reviewed to ensure that it is line with current safe practice and all risks minimised * (S)AEs will be reviewed throughout the trial period and any new risks identified will be addressed | | | | |

* 1. Appendix 2 - Trial management / responsibilities
     1. Patient registration/randomisation procedure

Patient registration and randomization will occur via the REDCap database (https://sscmredcap.bris.ac.uk/redcap).

All screened patients should be entered into the REDCap database, and all will receive a trial ID regardless of screening outcome.

* + 1. Data management

Data management is a local responsibility however database entry accuracy will be assessed. The CRFs and database will be designed to minimize scope for error in data recording. Any errors identified will be highlighted and communicated to the responsible local site to be corrected within a stated timeframe. Where applicable, a random sample of x% (at least 10%) of CRFs will be checked, by the trial research team or R&I monitor, against entries within the database and with the source data for quality purposes. The percentage checked will be increased if a significant error rate is found. The data from the first patient recruited at a new site will be reviewed. This may include consent records, safety data and primary endpoint data.

* + 1. Preparation and submission of Annual Safety Report/Annual

An annual trial report and regular newsletter will be prepared and disseminated by the trial coordinator.

* + 1. Data protection/confidentiality

Data will be handled in line with relevant laws and guidelines. Confidentiality will be maintained throughout and participant documentation will be stored and disposed of in line with national guidelines. Trial publications will contain no patient identifiable data.

* + 1. Trial documentation and archiving

Sites will locally archive trial data hard copies. The REDCap database will be maintained by North Bristol NHS Trust.

* 1. Appendix 3 – Authorisation of participating sites
     1. Required documentation
        + Confirmation of Capacity and Capability
        + CV and GCP certificate of local Principal Investigator
        + Signed mNCA (Participating Site Agreement).
     2. Procedure for initiating/opening a new site

SIVs are planned to occur via teleconference or local visit.

Steritalc is freely available and it is expected that sites will source their own supply.

IPC catheters and consumables will be sent to sites prior to coming on line.

The ‘Green Light’ will be issued by sponsor once all required documentation has been received and an SIV has occurred.

* + 1. Principal Investigator responsibilities

The PI’s legal responsibilities will be listed in the Participating Site Agreement.

* 1. Appendix 4 – Schedule of Procedures

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Procedures/assessments** |  | | | **Visits** | | | | | | | |
| **Screening** | **Consent / Baseline / Randomisation** | **Procedure** | | **IPC arm only** | | **Follow up visits** | | | | |
| **Talc instillation** | **Talc instillation + 1 day** | **Week 2** | **Week 4** | **Week 8** | **Week 12** | **Throughout trial** |
|  |  | **Up to -28 days** | **Day 0** | | **Day 7 ± 3** | **Day 8 ± 0** | **± 3** | **± 3** | **± 7** | **± 7** |  |
| Eligibility assessment | X | X |  | |  |  |  |  |  |  |  |
| Informed consent |  | X |  | |  |  |  |  |  |  |  |
| Demographics and Medical History | X | X |  | |  |  |  |  |  |  |  |
| Clinical assessment | X | X | X | | X | X | X | X |  | X |  |
| Observations |  | X | X | | X |  | X | X |  | X |  |
| Imaging - Thoracic Ultrasound |  | X |  | | X |  | X | X |  | X |  |
| Imaging - Chest X-ray1 | X | X | X | | X |  | X | X |  | X |  |
| Standard bloods |  | X2 |  | |  |  | X | X |  | X |  |
| Concomitant medications | X | X |  | |  |  | X | X | X | X |  |
| Randomisation |  | X |  | |  |  |  |  |  |  |  |
| IPC insertion |  |  | X | |  |  |  |  |  |  |  |
| Therapeutic Aspiration |  |  | X | |  |  |  |  |  |  | X6 |
| Instillation of talc |  |  |  | | X |  |  |  |  |  |  |
| IPC drainages |  |  | X | | X | X | X | X |  | X | X4 |
| Renal function monitoring5 |  |  | X | | X | X |  |  |  |  |  |
| PROMS(VAS, EQ5D and MLHFQ) |  | X | X8 | |  |  | X | X |  | X | X3 |
| Healthcare utilisation |  |  |  | |  |  | X | X | X | X |  |
| Adverse event assessments |  |  | X | | X | X | X | X | X | X |  |
| Pleurodesis assessment |  |  |  | |  |  |  |  |  |  | X7 |
| Semi-structured interview |  |  |  | |  |  |  |  |  |  | X |

1See 7.6.7 Chest x-rays

2Required to be taken within 3 months

3Self-reported VAS scores measured at baseline, daily from Day 0 to 14, then weekly for the remainder of follow up

4See 7.6.4 Community IPC Drainages

5Twice weekly for 2 weeks post procedure (only in patients with an IPC in situ) see 7.6.3

6Ad hoc

7See 7.7 Pleurodesis

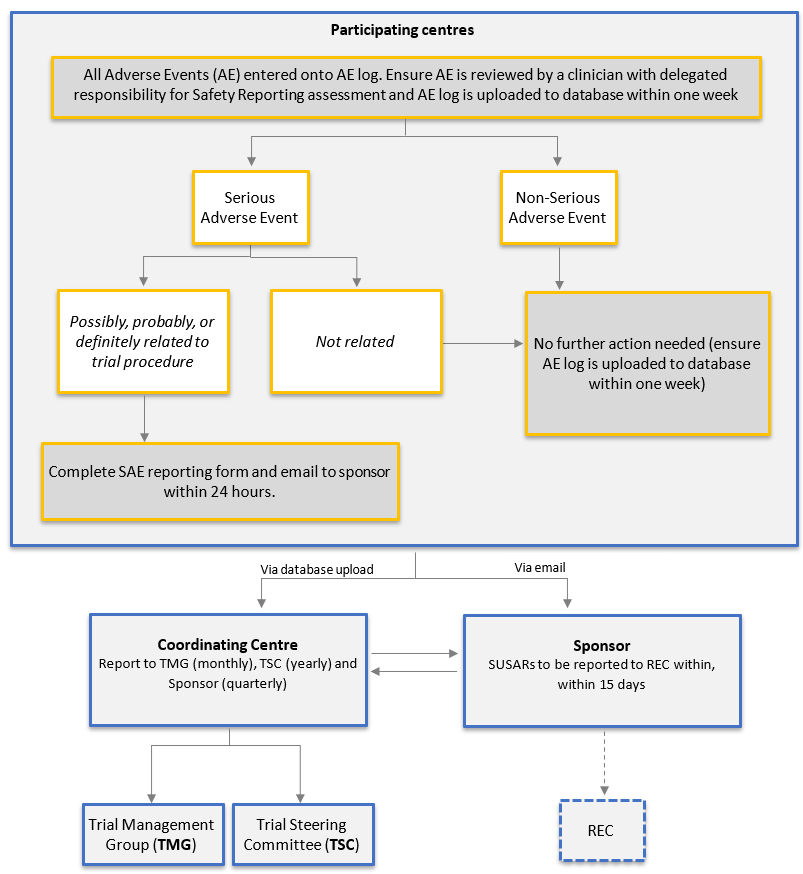
8 VAS only

* 1. Appendix 5 – Daily Schedule of IPC drainages

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Day** | **Visit** | **Requested drainage schedule** | **Minimum District Nurse drainage** | **Drainage regimen** |  | **Day** | **Visit** | **Requested drainage schedule** | **Minimum District Nurse drainage** | **Drainage regimen** |
| 0 | Procedure | 1 |  | Daily drainage (min 5/week) |  | 42 |  |  |  | Min 2/week |
| 1 |  | 1 | 1 |  | 43 |  |  |  |
| 2 |  | 1 |  |  | 44 |  |  |  |
| 3 |  | 1 | 1 |  | 45 |  | 1 | 1 |
| 4 |  | 1 |  |  | 46 |  |  |  |
| 5 |  | 1 | 1 |  | 47 |  |  |  |
| 6 |  | 1 | 1 |  | 48 |  | 1 | 1 |
| 7 | Talc instillation | 1 |  |  | 49 |  |  |  |
| 8 | Talc instillation +1 | 1 |  |  | 50 |  |  |  |
| 9 |  | 1 | 1 |  | 51 |  |  |  |
| 10 |  | 1 |  |  | 52 |  | 1 | 1 |
| 11 |  | 1 | 1 |  | 53 |  |  |  |
| 12 |  | 1 |  |  | 54 |  |  |  |
| 13 |  | 1 | 1 |  | 55 |  | 1 | 1 |
| 14 | 2 week FU | 1 |  |  | 56 | Remote FU |  |  |
| 15 |  | 1 | 1 |  | 57 |  |  |  |
| 16 |  | 1 | 1 |  | 58 |  |  |  |
| 17 |  | 1 |  |  | 59 |  | 1 | 1 |
| 18 |  | 1 | 1 |  | 60 |  |  |  |
| 19 |  | 1 |  |  | 61 |  |  |  |
| 20 |  | 1 | 1 |  | 62 |  | 1 | 1 |
| 21 |  |  |  | Min 3/week |  | 63 |  |  |  |
| 22 |  |  |  |  | 64 |  |  |  |
| 23 |  | 1 | 1 |  | 65 |  |  |  |
| 24 |  |  |  |  | 66 |  | 1 | 1 |
| 25 |  | 1 | 1 |  | 67 |  |  |  |
| 26 |  |  |  |  | 68 |  |  |  |
| 27 |  | 1 | 1 |  | 69 |  | 1 | 1 |
| 28 | 4 week FU | 1 |  | Min 2/week |  | 70 |  |  |  |
| 29 |  |  |  |  | 71 |  |  |  |
| 30 |  |  |  |  | 72 |  |  |  |
| 31 |  | 1 | 1 |  | 73 |  | 1 | 1 |
| 32 |  |  |  |  | 74 |  |  |  |
| 33 |  |  |  |  | 75 |  |  |  |
| 34 |  | 1 | 1 |  | 76 |  | 1 | 1 |
| 35 |  |  |  |  | 77 |  |  |  |
| 36 |  |  |  |  | 78 |  |  |  |
| 37 |  |  |  |  | 79 |  |  |  |
| 38 |  | 1 | 1 |  | 80 |  | 1 | 1 |
| 39 |  |  |  |  | 81 |  |  |  |
| 40 |  |  |  |  | 82 |  |  |  |
| 41 |  | 1 | 1 |  | 83 |  | 1 | 1 |
|  |  |  |  |  |  | 84 | 12 week FU | 1 |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  | **Total drainages** | **40** | **30** |  |

* 1. Appendix 6 – Safety Reporting Flow Chart

See <https://www.nbt.nhs.uk/research-innovation/research-policies-forms/standard-operating-procedures> for current Safety Reporting SOP and reporting forms.



* 1. Appendix 7 – Amendment History

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
| NA | 1.1 | NA | Emma Keenan | Minor inconsistencies corrected pre final REC approval |

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