This supplement contains the following items:

Section 1

a) Original protocol

b) Final protocol

c) Summary of changes.

Section 2

a) Original statistical analysis plan

b) Final statistical analysis plan

c) Summary of changes.

Section 1a – Original protocol

North Bristol NHS
NHS Trust

The efficacy of Indwelling Pleural Catheter placement versus IPC placement PLUS sclerosant (talc) in patients with malignant pleural effusions managed exclusively as out-patients

[IPC-PLUS Trial]

Protocol

A single-blind, randomised controlled trial to determine the most effective method for management of malignant pleural effusions using indwelling pleural catheters.

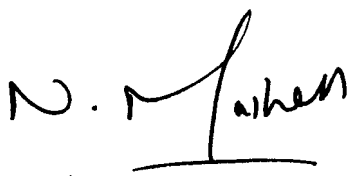
Chief Investigator	**Dr. Nick Maskell**
Trial Protocol Version	**1**
Version date	**10/04/2012**
R&I number	**2795**
REC	**12/SC/0242**
EudraCT Number	**2012-000599-40**

Authorised by:

Name: Dr Nick Maskell

Role: Chief Investigator

Date: 10th April 2012



SIGNATURE

GENERAL INFORMATION

This document describes the IPC-PLUS trial and provides information about procedures for entering patients into it; the protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its creation, but corrections or amendments may be necessary.

COMPLIANCE

The trial will be conducted in compliance with the protocol, Research Governance Framework, Data Protection Act and other guidelines as appropriate.

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CONTENTS

SECTION 1 – ABSTRACT AND TRIAL DESIGN

1.1
Abstract

Malignant pleural effusions remain a common problem with 40,000 new cases in the UK each year and up to 250,000 in the US [1]. They are increasing in incidence as survival rates of most cancers improve and life expectancy rises.

Controlling patients' symptoms of breathlessness by removal of the pleural fluid is the cornerstone of patient management, but these effusions will usually recur without more definitive intervention.

Traditional management of malignant pleural effusions has involved an inpatient stay with placement of a chest drain. This can then be followed by instillation of a pleural sclerosing agent such as talc, which aims to minimise further fluid build-up. Despite a good success rate in studies, this approach can be expensive, time-consuming and inconvenient for patients. More recently, an alternative method has become available in the form of indwelling pleural catheters which can be inserted and managed in an outpatient setting. They have also been shown to induce a pleurodesis in a small proportion of patients, but over a longer period of time.

Theoretically, therefore, the combination of indwelling pleural catheters and talc pleurodesis through this tube should provide the optimum management for malignant pleural effusions, with improved convenience for patients and a higher pleural symphysis rate.

We aim to prove, by way of a single-blind, multicentre randomised controlled trial, that this combination of treatments is superior to the use of indwelling pleural catheters alone. This study will recruit 154 patients and will assess the proportion of patients with successful pleurodesis at 5 weeks post randomisation. This study aims to help to define the future gold-standard out-patient management for patients with symptomatic malignant pleural effusions.

1.2
Lay summary

Many people with cancers (malignancies) can develop fluid in the space between the lung and the chest wall, known as the pleural space. This may be due to a tumour which directly affects the lung lining (the pleura), such as a mesothelioma, or another cancer from elsewhere which spreads to affect the pleura. If enough fluid accumulates the lung can be compressed, making patients feel significantly breathless. This fluid is termed a malignant pleural effusion.

The traditional method for dealing with this fluid is to admit the patient to hospital and insert a chest tube into the space around the lung where the fluid has built up. This allows the fluid to be drained away in the first instance, alleviating symptoms. However, after the tube is removed, this fluid may build up again. This usually takes some time but can occur in

only a few days. In order to try and prevent this re-accumulation, an irritant substance such as talc powder can be inserted through the chest tube. This aims to cause the two sides of the pleural space to stick together which obliterates the area in which fluid might build up. This is called pleurodesis. Whilst often relatively successful, this method of pleurodesis can be inconvenient for patients as they often need to be in hospital for at least 5 days.

In recent years an alternative method has become available. This involves the insertion of a chest tube, which is tunnelled under the skin, and hence can stay in place for much longer. Their main benefit is that they can be inserted as an outpatient and as more fluid builds up it can be tapped off, using the drain, as needed by community nurses. In the United States, these indwelling pleural catheters (IPC) are often the first line of treatment for malignant pleural effusions. Another benefit is that if left long enough, these tubes can also cause the pleural surfaces to adhere to each other and so may actually prevent further fluid build-up in much the same way as talc can. The rate of pleurodesis, however, is not as high as with talc, and if used for more than a few weeks the cost of using the IPC begins to exceed that of traditional treatment.

Our study aims to help determine the optimum management of patients with malignant pleural effusions by treating people with a combination of both indwelling pleural catheter and talc instillation. We shall compare the rates of pleurodesis at five weeks post randomisation, as well as patient reported outcomes and survival, with those treated with just a pleural catheter alone. In theory the addition of talc should improve time to pleurodesis, which would allow these catheters to be removed from patients more quickly. Although this study will look at patients from the UK, the results will be applicable globally and may help to change the way in which malignant pleural effusions are managed.

1.3
Study design

1.3.1
Trial type

Multi-centre, single-blind, randomised controlled trial to evaluate whether the combination of an indwelling pleural catheter and subsequent instillation of talc slurry is more effective at inducing pleurodesis than the use of an indwelling pleural catheter alone in the management of malignant pleural effusions in outpatients.

1.3.2
Disease / patients studied

The recruitment target is 154 participants. Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT) and through routine clinic appointments. Patients will be screened using the inclusion and exclusion criteria (see section 3.2 and 3.3). Eligible patients will be invited to participate on a consecutive basis. Participation in the trial will be discussed with the patient at the appropriate routine outpatient appointment. They will be allowed at least 24 hours to consider trial entry. Full written, informed consent will be obtained prior to enrolment.

1.3.3
Trial treatments

All patients will have an IPC inserted as per normal practice. Those eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant via the IPC (intervention group), or to receive a pleural placebo instillation of 0.9% sterile saline (control group).

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

Treatment allocation will be performed by Sealed Envelope Randomisation Services, an independent randomisation service. Minimisation with a random element will be used.

The minimisation factors are:

- Volume of pleural fluid removed in the first 10 days post IPC (≤1999 mls or ≥2000 mls)
- Malignancy subtype (Ovarian and breast; mesothelioma; other)
- Day 10 chest x-ray appearance (expanded with no evidence of trapped lung or evidence of trapped lung but fits the criteria for randomisation)

1.3.4
Outcome measures

Primary endpoint

1. The number of patients with successful pleurodesis at 5 weeks post randomisation.

Secondary endpoints

1. Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using:
    a. SF-36 health questionnaire
    b. EQ-5D health questionnaire
2. Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for
    a. Thoracic pain
    b. Breathlessness
3. Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
4. All-cause mortality up to 10 weeks post randomisation.
5. Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
6. Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at two-weekly intervals for 10 follow-up period
7. Pleurodesis success at 10 weeks post randomisation
8. Time from randomisation to successful pleurodesis, up to 10 weeks

1.3.5
Trial duration

Study follow-up will last until death or 10 weeks post randomisation, whichever is sooner. Patients will have an IPC inserted and will be randomised, if eligible, ten days later. They will then be reviewed at two weekly intervals. Patients will undergo IPC drainage in the community at least twice per week, with drainage volumes recorded at each occasion.

1.3.6
Investigational product

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. 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.

For the purposes of this trial, the intervention arm of the study will receive a talc slurry instillation ten days after IPC insertion, via the IPC. The slurry will consist of 4 grams of talc mixed with 50 mls of 0.9% saline. Those in the control arm will receive a placebo instillation of 50mls of 0.9% saline in lieu of talc slurry.

Intrapleural lidocaine of at a dose of 3mg/kg (to a maximum of 250mg) will also be given to patients in both arms.

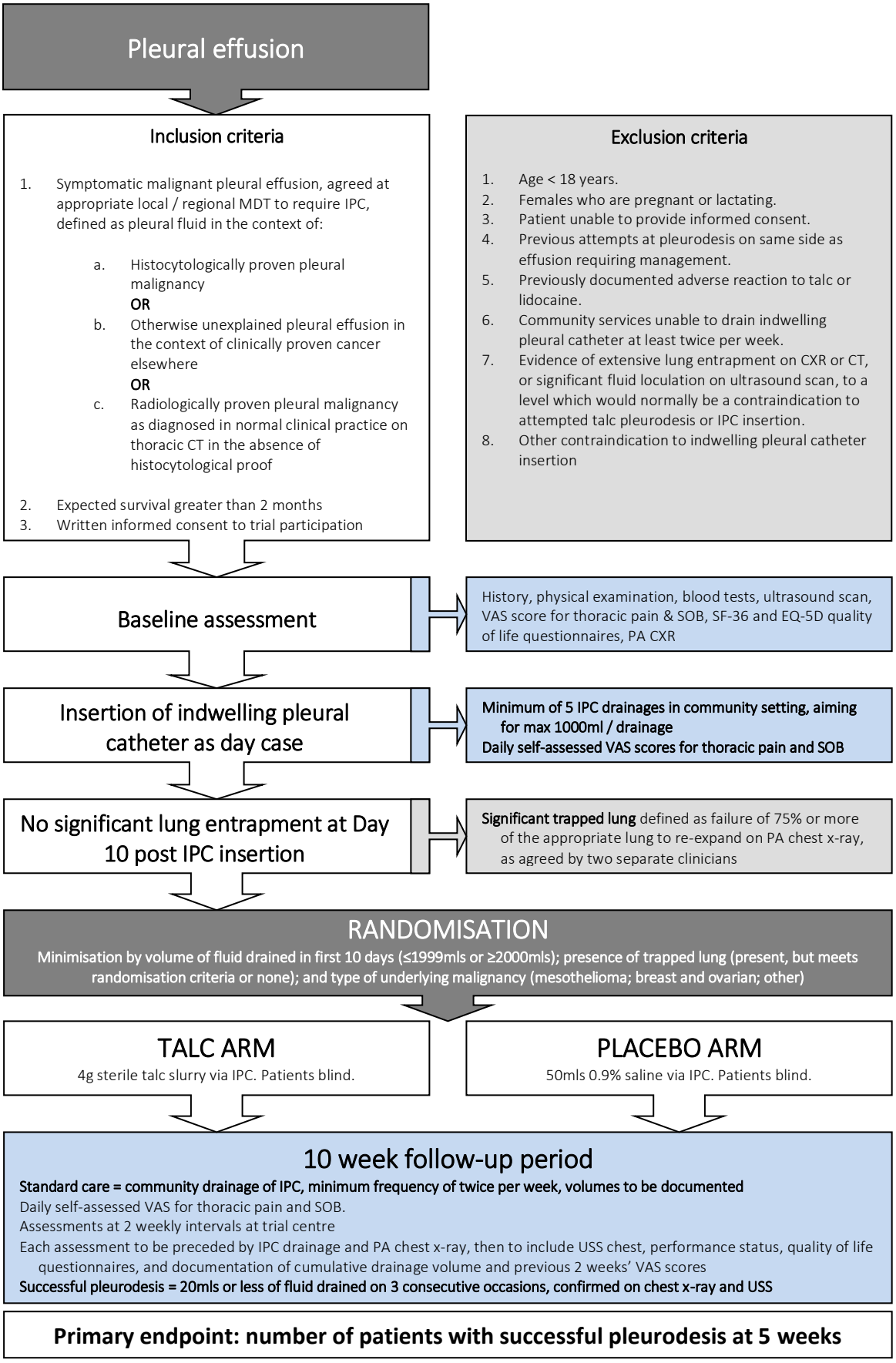
1.3.7
Trial centres

This trial will recruit initially from multiple NHS hospitals in England. All of the hospitals involved have dedicated pleural services and have a successful track record of recruiting to pleural clinical trials. The lead centre will be North Bristol and the trial will be co-ordinated by a clinical research fellow based there, who will be responsible for trial setup, delivery, liaison and query resolution at the other sites. Contact details for the individual centres are provided above.

1.3.8
Trial sponsor

The study is sponsored by North Bristol NHS Trust, who will oversee and ensure the compliance and integrity of the trial.

1.4
Trial flowchart



SECTION 2 - BACKGROUND

2.1
Scientific summary

Malignant pleural effusions (MPE) are a common complication of many cancers. Their presence usually indicates metastatic disease, and hence possibly a poorer prognosis. The majority of cases are due to lung cancer in men and breast cancer in women [4], although many other malignant processes can lead to fluid developing, including primary pleural disease such as mesothelioma or more generalised processes such as lymphoma [2].
In order for an effusion to be formally defined as malignant, there should be direct histological or cytological evidence of tumour in either the pleura or the fluid itself. However, the mean sensitivity of cytological examination is around 60% [5] and pleural biopsy is not always possible. Histology from the primary tumour, in combination with fluid biochemistry, is also therefore often used to make the diagnosis.

Since the primary malignant source of these effusions can be varied, it can be difficult to reliably predict survival based on their presence alone. Median survival has approached 2 years in some series [3] but the typical figure is generally lower at 4 to 12 months [6,7]. Patients with a hormone sensitive tumour, such as breast cancer, tend to have a better outcome.

The rate of fluid production may be determined by many factors, including underlying tumour type, but these are not yet well understood. Local audit data has suggested that serum levels of NT-ProBNP may have a predictive role in fluid volumes, and could therefore be used to guide patients' treatment. NT-ProBNP is a polypeptide which is secreted alongside BNP (brain natriuretic peptide) in response to pathological myocardial stretch. It has been shown to be of value as a negatively predictive test for the presence of heart failure [8] and has become more widely used by community medical services.

The traditional management of malignant effusions involves inpatient insertion of a chest drain, to ensure fluid drainage and pleural apposition, before the instillation of a sclerosant substance to cause pleural inflammation and adhesion. This aims to obliterate the pleural space and thus fluid build-up, and is known as chemical pleurodesis. Many substances can be used as a pleural irritant although by far the most commonly used is talc, which has been shown to be superior to alternatives such as tetracycline or bleomycin [9].

Talc is predominantly hydrated magnesium silicate and has been used for the purposes of pleurodesis since the 1930s [10]. For many years ungraded talc was used but this was associated with instances of severe inflammatory response, both systemically and locally [11, 12], which were later confirmed experimentally. Subsequent evidence has however shown that graded large-particle, sterile talc can be both safe and effective if used in doses up to 4 grams [13], and this is now the standard for chemical pleurodesis across much of the United Kingdom. It may be instilled using a chest drain in the form of a slurry, or can be sprayed thoracoscopically under direct vision. The thoracoscopic approach was not shown to be superior in a Cochrane review [9] and this was backed up by a recent large US-based RCT [14].

Pleurodesis success rates quoted in studies are typically high with talc, ranging from 81% to 100% [15], although these figures may vary considerably in real-world practice due to

differences between clinicians and individual centres. To achieve such efficacy a patient is typically admitted for insertion of a chest tube and drainage. Only once the pleural space is felt to be dry is talc inserted. This usually requires an inpatient stay of 5-7 days [16], often with at least 24 hours of pleural suction, and has significant health economic impact as well as the potential to impair the quality of life of patients with more limited life spans. Following the widespread use of large-particle talc, the side effects of pleurodesis have tended to be minor, the commonest being fever, pain and gastrointestinal upset [9,17,18], although there have been rare cases of empyema [19]. For this reason the routine use of sterile technique and analgesia is recommended when pleurodesis is attempted, including premedication with intrapleural lidocaine [15]. It should also be noted that, in those with malignant pleural effusions, there has been no documented increase in mortality by the use of talc pleurodesis over the use of either alternative agents or chest drains alone [9].

The main drawback of the traditional method of pleurodesis is the length of hospital stay and the inconvenience to patients. In more recent years, the use of indwelling pleural catheters has become more widespread and has brought the potential to alleviate these problems.

Indwelling pleural catheters (IPC) are silastic tubes, which have the potential to be left in place for weeks to months after being tunnelled under the skin. They can be inserted, with the appropriate training, under local anaesthetic or at thoracoscopy, and can even be performed as a day-case [20]. Once at home, the aim is to drain fluid regularly (usually three times per week) in the patient's own environment. This maximises the opportunity for pleural apposition and adhesion which potentially leads to complete pleurodesis – the presence of foreign material in the pleural space contributes to this. Drainage can be performed by anyone with appropriate training – the patient included – but is often managed by district nursing teams.

IPCs have been shown to be effective in the management of malignant pleural effusions, although there is a paucity of evidence comparing them directly to talc pleurodesis. In a retrospective series of 250 cases, almost 90% of patients experienced complete or partial relief of dyspnoea [21], a finding bettered in a later study in which all patients experienced improvement [22]. A recent meta-analysis has confirmed an overall 96% symptom improvement rate [23]. Indwelling drains have also been shown to improve more formal quality of life scores, even in comparison to talc pleurodesis [24]. Length of hospital stay can be significantly reduced when compared to traditional methods, one study demonstrating a five-day reduction in average inpatient time in the IPC group [25]. Despite the need for proprietary drainage kits they can also be cheaper overall to healthcare providers if used for less than 6 weeks [26]. This is an achievable goal as IPCs can often be removed following cessation of drainable fluid, a reliable surrogate indicator for pleurodesis. Such spontaneous pleurodesis generally occurs in around 50% of cases [21,22,27] and is heavily influenced by the underlying tumour type [28], although rates as high as 70% were reported in one study [29]. This group, however, had a mean time to pleurodesis of 90 days; the typical length of time to achieving pleural fusion commonly being quoted as one to two months [21,28]. The presence of 'trapped lung' (visceral pleural scarring) can lead to incomplete expansion following drainage, and may be an indication for insertion of an indwelling pleural catheter, which no doubt influences the variability of the time to pleurodesis in these studies. In patients with

these conditions, the failure of pleural apposition makes pleurodesis extremely unlikely as an enlarged pleural space persists even with drainage.

Pleural pressure measurement has been available for many years and can help in determining if there is likely to be abnormal lung expansion. Normal pressures can be difficult to determine but they are felt to represent a balance between the elastic recoil of the lung and the tendency of the chest wall to expand, with values typically being quoted as slightly sub-atmospheric (-3 to -5 cmH_20) [30].

During measurement, the manometer should be placed at the most dependent part of the fluid as this allows the maximum volume of fluid to be removed, and ensures the minimum contact between the lung and the catheter, which in turn ensures that the pressure in the pleural space is recorded accurately [31].

Previous studies have analysed the changes in both pleural pressure and pleural elastance (change in pressure divided by the change in volume), and have suggested typical patterns for lungs with normal recoil properties; those with lung entrapment; and those with trapped lung. Patients with trapped lung will tend to have a low or negative initial pressure, which then drops off sharply. Entrapped lungs may have a normal initial curve followed by a sharp pressure drop as fluid is removed. Normal lungs should exhibit only minimal pressure change as fluid is removed, with values approaching normal towards the end of the drainage [32].

A study by Lan et al. looked at pleural elastance during thoracentesis, to act as a surrogate for lung expansion. They found that an elastance of at least 19 cmH_20 after removal of 500mls of fluid predicted lung entrapment and therefore pleurodesis failure[33]. This situation is felt to be ideal for the use of IPCs as recurrent fluid accumulation is much more likely.

Indwelling pleural catheters are not without drawbacks however. There may be significant pain associated with the immediate and short-term post procedure period, and in some cases pleural tract metastases have been documented, although this has rarely exceeded 3% [34] and is usually under 1% [23]. In addition, their insertion requires specific training, which still does not guarantee success – a failure rate of 4% was documented in the largest series to date. This same group reported other complications including empyema formation (3%); secondary fluid loculation (12%), and cellulitis (2%) [21]. Nevertheless, meta-analysis data has shown IPCs are generally safe to use, with an overall complication rate of 12.5% [23].

It would seem, therefore, that the optimal approach to the management of malignant pleural effusions should be the combination of talc instillation, to achieve the highest pleurodesis rates, and placement of an indwelling pleural catheter to allow greater convenience and quality of life for the patient, and potentially lower healthcare costs. Despite the potential for combining these methods having been recognised [35] there have been no studies to date to test this hypothesis, although ambulatory pleurodesis for malignant effusions was attempted in one small series by Saffran et al [36]. A closed-system pigtail catheter was inserted and pleurodesis was attempted at a later date using 4 grams of talc. Patients were managed as outpatients and the authors describe their method as being a viable alternative to traditional inpatient management. However, patient numbers were

limited to 10 and there was no attempt at randomisation. The study took place before the widespread introduction of IPCs.

The IPC-PLUS trial aims to test the hypothesis that the combination of an IPC plus talc sclerosant is superior to an IPC alone in the management of malignant pleural effusions. This trial has the potential to significantly affect the way in which such effusions are managed in the future, on a global scale.

2.2
Research questions

2.2.1
Primary research question

In patients with a proven malignant pleural effusion;

1. Does the use of talc as a sclerosant in conjunction with an indwelling pleural catheter (IPC) increase the number of patients achieving successful pleurodesis, when compared to using an IPC alone?

2.2.2
Secondary research questions

1. Does using talc and an IPC together alter the amount of pain and breathlessness a patient experiences, when compared to using an IPC alone?

2. Does the use of talc and an IPC together alter a patient's quality of life, when compared to using an IPC alone?

3. What are the medical complications of using talc in conjunction with an IPC?

4. What are the logistical and clinical difficulties with using talc in conjunction with an IPC?

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 (BNP) correlate with the volume of pleural fluid drained and chance of successful pleurodesis?

7. Does pleural elastance during initial drainage correlate with lung entrapment and the chance of successful pleurodesis?

8. Is using talc in combination with IPC cost-effective when compared to IPC alone?

SECTION 3 – PATIENT SELECTION

3.1
Setting

Patients will be recruited from multiple centres in the UK. The trial is supported by the appropriate local and regional cancer networks.

Clinical care, drain insertion and imaging will be provided by local medical professionals at the patients' base hospitals. 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 by appropriately trained staff such as district nurses, lung cancer specialist nurses, or research nurses. The specifics of follow-up are detailed in section 4.2.3.

3.2
Inclusion criteria

1. Symptomatic malignant pleural effusion, agreed at appropriate local / regional MDT to require an IPC, defined as pleural fluid in the context of;
    a. Histocytologically proven pleural malignancy
    OR
    b. Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere
    OR
    c. Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof

2. Expected survival greater than 2 months
3. Written informed consent to trial participation.

3.3
Exclusion criteria

1. Age < 18 years.
2. Females who are pregnant or lactating.
3. Patient unable to provide informed consent.
4. Previous attempts at pleurodesis on same side as effusion requiring management.
5. Previously documented adverse reaction to talc or lidocaine.
6. Community services unable to drain indwelling pleural catheter at least twice per week.
7. 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.
8. Other contraindication to indwelling pleural catheter insertion

3.4
Recruitment

The recruitment target is 154, although an interim analysis will take place after 100 patients are enrolled. The statistical justification for this is given in section 6.2. Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT). It is expected that the local thoracic MDTs and the regional mesothelioma MDTs will provide the highest number of patients. Patients will be screened using the inclusion / exclusion criteria as above. Screening logs documenting reasons for exclusions will be kept throughout the trial.

Eligible patients will be invited to participate on a consecutive basis, and will be provided with an information leaflet at the earliest opportunity. Participation in the trial will be discussed with the patient at the appropriate outpatient appointment, which will form part of their normal care pathway. They will be allowed at least 24 hours to consider trial entry, as well as to ask questions of investigators. Full written, informed consent will be obtained prior to enrolment.

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

3.5
Co-enrolment guidelines

For the duration of a patient's involvement with IPC-PLUS data collection, they should not be entered into any other clinical trial which attempts to directly affect pleural fluid production, management or drainage. Oncological management of the underlying disease will be guided by the site-specific cancer MDTs, and any treatments or entry into relevant systemic anti-cancer trials will not be restricted. Should a participant be considered for co-enrolment in another trial of any origin then liaison with the IPC-PLUS trial team is essential to ensure compatibility between the trial protocols.

Once a patient has had their drain removed any further management, including the repeat use of IPC, will be at the discretion of local clinicians. However, patients may only be enrolled in the IPC-PLUS trial once.

SECTION 4 – ASSESSMENT AND TREATMENT OF PATIENTS

4.1
Standard care

All patients will be discussed in their local thoracic MDT, or, if the underlying malignancy is not pulmonary, an appropriate specialist MDT. Mesothelioma patients will be discussed at a regional MDT if available. Patients will be referred to their local oncologist for discussion and consideration of their treatment options in the usual manner. For all issues other than those pertaining to the drainage of the malignant pleural effusion, treatment discretion lies with the primary physician, surgeon or team.

Normal clinical review will take place in the usual oncology or respiratory clinic. The frequency of clinical review will depend on patient choice, severity of symptoms and clinical discretion. In general, patients who are managed with chemotherapy for underlying malignancy are reviewed every 2-3 months.

All attempts should be made to co-ordinate trial follow-up and routine follow-up appointments. Patients should be given contact details for an appropriate specialist nurse at the earliest opportunity.

Patients will usually be offered placement of an indwelling pleural catheter by a respiratory team.

4.2
Trial interventions

4.2.1
Pre-randomisation

Interventions and procedures to be performed during the pre-randomisation period are summarised in table 1.

Potential patients will be screened as described above. Those who may be suitable for an IPC will have this option discussed in a normal outpatient setting, where they will also be given the option of participating in the IPC-PLUS trial. A written information sheet should be provided to those who are initially eligible and willing to be entered. They will then be given at least 24 hours to consider the information provided and to decide whether they wish to participate in the trial. Sufficient time will be allowed for questions and answers prior to written, informed consent being taken.

Consent for trial entry must be taken by a member of the trial team and should take place before the placement of the patient's IPC. The most convenient opportunity may be at the same time as consent is taken for the IPC insertion.

Prior to consent being taken, the patient should undergo a routine thoracic USS looking for evidence of significant loculation to ensure IPC insertion, and trial entry, are still appropriate.

Once an eligible patient is consented, a baseline assessment will be undertaken by a member of the trial team and entered onto the appropriate Case Report Form (CRF). Much of this information may already be available from recent consultations and will include:

- Relevant medical history and physical examination, to include;
    - Onset and nature of symptoms
    - Type of malignancy causing effusion (if known)
    - Pleural procedures to date
    - Current ECOG / WHO performance status
    - Current analgesia history
    - Current and projected treatment plan outside of IPC-PLUS
    - History of adverse reactions to medications
- Standard blood tests
- Visual-Analogue Scale (VAS) score to assess thoracic pain and breathlessness
- Quality of life assessment using SF-36 and EQ-5D health questionnaires
- PA Chest x-ray
- Thoracic ultrasound scan with loculation score

Along with the standard blood tests, two serum EDTA tubes, one serum gel tube, and one lithium heparin tube of blood should be taken for centrifuge and storage, to allow processing of NT-ProBNP at a later date.

Patients will then be given an appointment, if this has not already been provided, to have an indwelling pleural catheter inserted as a day case procedure. This should be within one week of the baseline assessment. If an appointment cannot be made within this time, this should be recorded as a protocol deviation and reported to the trial co-ordinator or trial administrator.

IPCs must be placed by an appropriately trained member of staff, but not necessarily a member of the trial team. The IPC insertion CRF should be completed during or immediately after the procedure. Immediately following drain placement, up to 1000mls of pleural fluid should be removed using the appropriate adaptor kit. This should be done with the patient positioned so as to ensure the drain is in a dependent position. During this procedure pleural pressures should be measured, using a calibrated pleural manometer, after every 100mls removed. These recordings should be entered onto the case report form (CRF) and the total volume removed recorded in the patient's drainage booklet. Fluid samples should be collected and sent in two EDTA blood tubes, one serum gel tube, and one lithium heparin tube for centrifuge and storage alongside the aforementioned blood samples.

A chest x-ray should be performed post-procedure to confirm adequate drain placement.

Prior to discharge, the patient will be issued with a drainage booklet which will act as a record for the volumes of fluid drained throughout their period of trial participation. They will also be given a chart on which they can complete their own VAS scores for pain and breathlessness, which should be done on a daily basis. They should be given an appointment for follow-up in 10 days.

For the period following discharge and before their first appointment at day 10 post IPC insertion, patients should have their fluid drained on at least 5 occasions, the initial drainage being immediately after IPC insertion by the person inserting it. Subsequent drainages will ideally be performed in the community by appropriately trained staff such as district nurses, research nurses or lung cancer specialist nurses. Patients will also have a drainage performed immediately prior to their first post-IPC appointment. Any person who is to perform drainage should have been adequately trained, ideally by a member of the trial team. The initial target drainage volume should be a maximum of 1000mls on each occasion with the aim being to ensure the pleural cavity is as dry as possible prior to sclerosant instillation. After each drainage the volume removed should be recorded by the person removing the fluid.

Patients will attend their local trial centre 10 days after IPC insertion. Once they have had their fluid drained as described above they should undergo a PA chest x-ray and have an appointment with a member of the trial team, who will perform a medical assessment as outlined on the appropriate CRF. Quality of life will be assessed using the questionnaires described above. The chest x-ray should be examined for evidence of lung entrapment. A thoracic ultrasound of the side where the IPC has been inserted should be performed, looking for evidence of fluid loculation and septation. A septation score should be documented (see appendix). The amount of fluid loculation or septation should not influence randomisation at this point.

If there is evidence of significant lung entrapment (>25% of the hemi thorax with unexpanded lung on CXR as judged by two separate clinicians) then the patient should be excluded from randomisation. Should there be disagreement regarding the degree of lung entrapment on chest x-ray, then a third independent clinician should be enlisted to provide a casting vote.

If a patient is eligible for trial entry at this point then they should be randomised at the same visit and given the allocated instillation substance before returning home.

Table 1 – Pre-randomisation action chart

Day(s)	Patient action	Trial team action	Community team action	Documents for trial team / nurses to complete	Documents for patient to complete	Tests / procedures performed	Location
0	Attend hospital Consent to trial involvement Consent to IPC insertion Complete VAS and QoL scores	Obtain consent for trial Obtain consent for IPC insertion Perform baseline assessment Insert IPC + drain <1L while recording manometry values Provide appointment for randomisation visit Liaise with community team to ensure drainage plan in place Provide drainage booklet Provide 2-week VAS chart Process trial samples		Consent form for trial Consent form for IPC Enrolment form Baseline CRF Manometry CRF Appointment card	Consent form for trial Consent form for IPC insertion VAS chart EQ-5D and SF-36	Chest x-ray Thoracic USS Standard blood tests Trial blood samples IPC inserted with manometry readings Trial pleural fluid samples	Day case
1 to 10	Complete daily VAS scores on chart provided	Support community team if needed with drainages of IPC	At least 5 drainages of IPC Document volumes in drainage booklet			Drainage of IPC	Community

4.2.2
Randomisation

Interventions and procedures to be performed during the randomisation and post randomisation periods are summarised in table 2.

Those eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant via the IPC, or to receive a pleural placebo instillation of 0.9% sterile saline. Treatment allocation will be performed by Sealed Envelope Randomisation Services (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA), an independent randomisation service. Minimisation with a random component will be used.

The minimisation factors are:

- Volume of pleural fluid removed in the first 10 days post IPC (≤1999 mls; ≥2000 mls)
- Malignancy subtype (Ovarian and breast; mesothelioma; other)
- Day 10 chest x-ray appearance (expanded with no evidence of trapped lung; evidence of trapped lung but fits the criteria for randomisation)

A member of the research team will contact the randomisation service as soon as lung entrapment is excluded.

4.2.3
Post-randomisation (instillate allocation and administration)

The allocated treatment substance must not be communicated to the patient. The procedure for the instillation of the allocated substance should remain the same for both groups, and is outlined in the appropriate standard operating procedure (SOP). Patients must be kept blind from the substance they are receiving by concealing the syringe with an opaque wrapping; by preparing the instillate in a separate room; and by administering the allocated substance from behind the patient, with the patient facing forward. All instillations should be followed by an adequate flush to ensure no trace of the allocated substance is left in the IPC line.

Patients will then be provided with a further self-assessment VAS sheet to encompass the next 14 days, and instructions should be given for this to be completed on a daily basis at the same time each day. They will also be given an appointment card which will outline the schedule for their follow-up period. This should be completed with details of their next appointment at each consultation prior to discharge. All patients will be issued with a standard amount of analgesia to take home, as outlined in the SOP.

Patients should be allowed home after an adequate period of observation post-instillation. This should be for a minimum of 2 hours and include at least half-hourly measurements of pulse, blood pressure, temperature, pain score and respiratory rate. Should there be evidence of significant systemic inflammation or significant pain, a medical decision should be made regarding whether admission to hospital for further assessment and treatment is required.

Table 2 – Randomisation and post-randomisation action chart

Day(s)	Patient action	Trial team action	Community team action	Documents for trial team / nurses to complete	Documents for patient to complete	Tests / procedures performed	Location
0	Attend for randomisation Provide completed VAS chart Provide up to date drainage booklet	Check x-ray for trapped lung **IF SUITABLE – RANDOMISE TO EITHER PLACEBO OR TALC** Document VAS from previous 10 days Provide appointment for Assessment 1 Provide 2-week VAS chart		Drainage booklet Randomisation form Appointment card	EQ-5D and SF-36	Drainage of IPC Trial pleural fluid samples Chest x-ray Thoracic USS **Instillation of either placebo or talc**	Outpatients
14, 28, 42, 56, 70	Attend for Assessment Provide completed VAS chart Provide up to date drainage booklet	Perform Assessment Perform USS and complete septation score Check chest x-ray Document VAS from previous 2 weeks and provide chart for further 2 weeks Provide appointment for next assessment (unless day 70)		Drainage booklet Assessment CRF Appointment card	EQ-5D and SF-36	Drainage of IPC Trial pleural fluid samples Chest x-ray Thoracic USS	Outpatients
0 to 70	Complete daily VAS chart and bring to each appointment	Support community team if needed with drainages of IPC	Drainage of IPC at least twice weekly			Drainage of IPC	Community

4.2.4
Community drainage

Following randomisation and the allocated instillation, all patients will receive fluid drainage in the community. This will be done by a person who has been appropriately trained, ideally by a member of the trial team. The frequency of drainage will be at the discretion of the patient and community team but should occur at least twice per week, and should begin at three times per week as per standard practice.

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

Patients will have been provided with a self-assessment VAS sheet for thoracic pain and breathlessness. This will cover the time period between outpatient visits and should be completed at the same time each day, ideally before a drainage takes place. Patients should bring this sheet, along with their drainage booklet, to each clinical assessment.

4.2.5
Clinical assessment (DAYS 14, 28, 42, 56, 70)

The follow-up period for each patient is 10 weeks post IPC insertion, or until death.

During this time, the first clinical assessment will occur two weeks after randomisation, and at two-weekly intervals thereafter, in the patient's base hospital. In the event that a patient is unable to attend for an outpatient assessment on the allocated day, an appointment should be provided for within 72 hours of the originally planned day and the delay documented on the appropriate CRF. If the patient cannot attend an appointment within this 72 hour window then another appointment should be made for as early as possible, and the delay reported to the trial administrator or trial co-ordinator as a protocol deviation.

Before the assessment but following arrival at the hospital, the IPC should be drained to dryness by a trained member of staff, with pleural fluid samples stored as detailed below. The assessment should then be completed on 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
- Complications of IPC placement through history and examination
- Documentation of analgesia requirements (DAY 14 only)
- Documentation of chemotherapy / radiotherapy and any response
- Current ECOG / WHO performance status
- Quality of life assessments using SF-36 and EQ-5D health questionnaires

At each visit, patients should also have a PA chest x-ray and undergo a thoracic ultrasound, specifically looking for the amount of loculation. This will be documented as a septation score.

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

4.2.6
Removal of drains

Once inserted, drains 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, on which investigators will need to clearly document the reason for the proposed removal. Potential reasons may include local subcutaneous or pleural infection, intolerable pain, significant fluid loculation, or cessation of fluid drainage. If an investigator wishes to remove an IPC for a reason not stated on trial documentation, then a member of the trial team should be informed before removal takes place.

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.

Any patient who has a drain removed will continue to undergo planned follow-up for the 70-day trial period.

4.2.7
Blockage of drains

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, perhaps due to cessation of drainage with persistent chest x-ray or ultrasound changes, then standard local unblocking procedures should be followed. This may involve a short hospital admission for administration of intrapleural urokinase. Such events should be documented on the appropriate CRF and, as per normal, in the patient's notes.

4.2.8
Biological samples and storage

During the pre-IPC baseline assessment, standard blood tests for full blood count, urea and electrolytes, liver function, clotting function and C-reactive protein will be taken. In addition to these, 2 EDTA, 1 serum gel tube, and 1 lithium heparin tube of blood will be taken. Shortly after, during IPC insertion, 2 EDTA, 1 serum gel tube, and 1 lithium heparin sample tube of pleural fluid will also be collected. All samples should be centrifuged at 1000g and the supernatant frozen at -80°C for future NT-ProBNP and cytokine analysis.

Prior to each trial follow-up appointment (every two weeks for 10 weeks), additional samples of pleural fluid should be collected during IPC drainage and processed in the same manner as above.

Participants will give their permission for linked anonymous blood and pleural samples to be stored and analysed at North Bristol NHS Trust (NBT), or, if from other sites, for those

samples to be transferred to NBT for storage and analysis. Samples will be stored in a dedicated Respiratory Research Unit freezer in the University of Bristol laboratory on the NBT site. Samples will be stored, anonymised and eventually destroyed in line with local policy

4.2.9
Ultrasound scans

All ultrasound scans will be performed by experienced and fully trained operators of the research team. Scans will be used to assess the presence and degree of pleural fluid complexity, and fluid depth (standard practice). A septation score will be awarded and documented (see appendix).

4.2.10
Visual Analogue Scale (VAS) scoring

VAS scores will be collected for each patient, beginning at their baseline assessment and ending when their follow-up is completed or is terminated due to death, withdrawal or ineligibility to undergo randomisation.

All patients will complete a VAS score for thoracic pain and breathlessness during their baseline assessment. After IPC insertion, beginning the following morning, patients should repeat these scores using the documentation provided. Similar VAS scores should be recorded on a daily basis for the duration of trial involvement, with recordings being made each morning. If IPC drainage is due to take place that day, then the score should be noted before the drainage takes place.

Patients will be provided with a chart which allows them to record VAS scores for 2 weeks. Completed charts should be brought to each trial follow-up assessment and will be replaced as needed. If a patient dies before all charts can be collected, these should be sent via mail to the local trial centre.

4.2.11
End of trial

The trial will cease recruitment once the target of 154 patients has been met, or if the trial steering committee feels the interim analysis after 100 patients justifies early cessation. The provisional end of trial (EoT) date will therefore be 10 weeks after the randomisation of the 154th trial patient. 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. This will require consent to be given separate to trial involvement.

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

4.2.12
Investigational product

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. 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 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.

For the purposes of this trial, the intervention arm of the study will receive a talc slurry instillation ten days after IPC insertion, via the IPC. The slurry will consist of 4 grams of talc mixed with 50 mls of 0.9% saline. Those in the control arm will receive a placebo instillation of 50mls of 0.9% saline in lieu of talc slurry, which is licenced as a vehicle for drug administration. This is manufactured by Baxter Healthcare Limited (Caxton Way, Thetford, Norfolk, IP24 3SE) and is marketed in the UK under the authorisation number PL 00116/0335. No adverse effects due to the use of 0.9% saline are anticipated.

SECTION 5 – PATIENT WITHDRAWAL AND FOLLOW-UP COMPLICATIONS

5.1
Patient withdrawal

Patients will have originally consented to trial follow-up, and to sample collection, storage and analysis. Patients 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 patient's CRF, and clarification on the nature of the withdrawal of consent, as outlined below, should be sought. Patients may still be stratified as 'alive' or 'dead' at the end of their follow-up period, unless consent for clinical data use is withdrawn. Patients who withdraw before randomisation will not be included in the final analysis.

5.1.1
Withdrawal of consent to all trial involvement

The patient 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.

5.1.2
Withdrawal of consent to follow-up and further clinical data collection only

The patient 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.

5.1.3
Withdrawal of consent to follow-up, further clinical data collection, and clinical data use
The patient withdraws consent to further follow-up visits, recording of clinical data, and the use of any clinical data already collected in analyses.
They maintain consent for blood and fluid samples already taken to be analysed.

5.1.4
Withdrawal of consent to sample analysis only
The patient withdraws consent for their previously taken blood and pleural samples to be analysed, or for any data already obtained from such samples to be used in the final analysis. Samples and associated data should be destroyed in line with local policy. They maintain consent for trial follow-up, clinical data collection and the use of this data in the final analysis.

5.2
Other follow-up complications

If a patient moves to another area outside the trial catchment, every effort should be made to continue follow-up in conjunction with the new local services, or via the new GP.

SECTION 6 – STATISTICAL CONSIDERATIONS

6.1
Outcome Measures

6.1.1
Primary endpoint

1. The number of patients with successful pleurodesis at 5 weeks post randomisation.

6.1.2
Secondary endpoints

1. Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using:
    a. SF-36 health questionnaire
    b. EQ-5D health questionnaire
2. Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for
    a. Thoracic pain
    b. Breathlessness
3. Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
4. All-cause mortality up to 10 weeks post randomisation.
5. Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
6. Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at two-weekly intervals for 10 follow-up period
7. Pleurodesis success at 10 weeks post randomisation
8. Time from randomisation to successful pleurodesis, up to 10 weeks

6.1.3
Successful pleurodesis

Successful pleurodesis will be defined as the collection of less than, or equal to, 20mls 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, who should be blind to treatment allocation. Information on drainage volumes will be collected in the community and during follow-up visits as described above. The x-ray for chest opacification must have been taken after the third consecutive occasion of collection less than 20mls, and within the 10 week follow-up period. All three occasions of collection less than 20mls should also occur within the 10 week follow-up period.

Patients who drain less than 20mls of fluid on three or more occasions but who continue to have greater than 25% pleural opacification on chest x-ray due to pleural fluid (as proven by thoracic ultrasound), will be defined as having an unsuccessful pleurodesis. If there is a clinical suspicion that the drain may be blocked then appropriate attempts to resolve this should be made prior to a definition being made.

The achievement of pleurodesis should be dated to the first drainage of less than or equal to 20mls. Even if patients achieve the requirements for pleurodesis during the trial period, they will continue to receive fortnightly follow-up as originally planned until the 70-day follow-up period is complete.

Patients who die during the 10-week trial period will be assessed for whether they achieved pleurodesis success prior to death. This requires the collection of less than, or equal to, 20mls 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, who should be blind to treatment allocation, with the x-ray having been taken after the third consecutive collection volume of less than 20mls.

6.1.4
Other outcome measures

1. Association between baseline levels of serum NT-ProBNP and pleurodesis success
2. Association between pleural elastance during initial fluid drainage and pleurodesis success

6.2
Sample size

Talc pleurodesis alone has been shown to be up to 90% efficacious in trial conditions [15], and we expect the combination of talc and IPC to be at least as effective as talc alone. IPCs used alone have a more variable range for pleurodesis efficacy but it is thought to be around 50% [21,22,27] for pulmonary or pleural malignancies, which are expected to make up the bulk of our trial cases.

In order to detect a 25% difference in pleurodesis success at 5 weeks (60% IPC alone vs 85% IPC and talc) with 90% power, a 5% significance level, and 5% loss to follow-up, we would require 154 patients (77 in each arm).

Based on current audit data, we expect each primary trial centre to see more than 8 potentially eligible patients per month. Therefore, assuming a consent rate of 35-50%, recruitment would take between 13 and 18 months.

6.3
Statistical analysis

The primary analysis will be by intention-to-treat, and will include all randomised patients on whom an outcome is available. All tests will be two-sided, and all analyses will be adjusted for the minimisation variables. Successful pleurodesis will be analysed using a logistic regression model.

A full statistical analysis plan will be written prior to data unblinding. This is considered version 0.1 of the analysis plan.

6.4
Interim analysis
The Independent Data Monitoring Committee (IDMC) will review the trial at regular intervals to assess patient safety. Additionally, one interim analysis will be carried out after 100 patients in order to test for efficacy. The O'Brien-Fleming stopping rule will be used, which requires a p-value of <0.005 for the primary endpoint in order to stop the trial early. If the trial is not stopped at the interim analysis, the O'Brien-Fleming rule requires a p-value of <0.048 at the final analysis in order to declare a statistically significant difference in the primary endpoint. The results of the interim analysis will be presented to the IDMC, who will make a recommendation to the Trial Steering Committee (TSC) as to whether the trial should stop early. This recommendation will also take into consideration other sources of evidence apart from the primary endpoint (e.g. secondary outcomes and safety data).

6.5
Health economic outcomes

The perspective adopted in the economic analysis will be that of the English National Health Service and Social Services. As a result we will collect information on the following resource use items:

1. *Intervention costs*. This will entail collecting information on talc, consumables and staff time. This information will be obtained by reviewing hospital records. Should a significant between-group difference in the rates of IPC blockage and drain removal occur, these will also be included in the intervention cost analysis.

2. *Follow-up costs*. This will entail collecting information on patients' use of hospital resources after randomisation. Information collected will include: inpatient stays, outpatient services, use of emergency departments and ambulance costs. Information on inpatient stays will be obtained by reviewing the administrative care records in each of the participating centres.

Resource use items will be priced using unit cost schedules and salary scales such as PSSRU, NHS Trust Financial Returns and NHS Reference costs. If necessary, finance departments at each of the study centres will be contacted to obtain unit cost information not included in these sources.

As the main outcome measure in the economic evaluation will be incremental cost per Quality-Adjusted Life Year (QALY) gained, generic quality of life information will be collected using the the EuroQol EQ-5D – a widely used generic multi-attribute utility scale – and the Short Form (36) Health Survey. These will be completed for each patient at baseline and at each hospital assessment (randomisation, and at days 14, 28, 42, 56 and 70 post-randomisation) to measure patients' general health related quality of life. For QALY construction, EQ-5D results will be translated into utility values using published UK population valuations. As a sensitivity analysis, quality of life will also be assessed using the

Short-Form 36 (SF-36) – another widely used generic multi-attribute scale. Responses to the SF-36 will be converted into utilities using the SF-6D.

SECTION 7 – ADVERSE EVENTS

7.1
Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or Serious Adverse Reaction: any untoward medical occurrence or effect that at any dose;

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs 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 of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

7.2
Causality

Most adverse events and adverse drug reactions that occur in this trial, whether they are serious or not, will be expected treatment-related toxicities due to the drugs used in this trial. The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in the table below. If any doubt about the causality exists the local investigator should inform the trial co-ordinator who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

7.2.1
Relationships

- Unrelated – there is no evidence of any causal relationship.
- Unlikely – there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
- Possible – there is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
- Probable – there is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definitely – there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- Not assessable - there is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3
Reporting procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the trial coordination centre in the first instance. A flowchart is provided to aid in the reporting procedures.

7.3.1
Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the toxicity section of the relevant case report form and sent to the trial coordination centre within one month of the form being due.

7.3.2
Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

In the case of a SAE occurring, an SAE form should be completed and faxed to the trial coordination centre for all SAEs within 24 hours. However, due to the proposed population of patients in this study, death and hospital admission due to co-morbidities are to be predictable and expected occurrences during the trial. The dates of such events should be recorded on CRFs but should not be reported as SAEs unless the local principal investigator feels there is a clear temporal or causal relationship to a trial intervention (i.e. IPC insertion or administration of talc). In addition, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

In the case of suspected unexpected serious adverse reactions (SUSAR), the staff at the site should either;

a) Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the trial coordination centre together with relevant treatment forms and anonymised copies of all relevant investigations.

b) Contact the trial coordination centre by phone and then send the completed SAE form to the trial coordination centre within the following 24 hours as above.

The trial coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the trial according to the following timelines: fatal and life-threatening within 7 days of notification; and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the trial. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs and SUSARs are as follows:

Fax: 0117 323 2947 (For attention of: IPC-PLUS Trial administrators)

Please send SAE forms to:
IPC-PLUS Trial,
Respiratory Research Unit,
Southmead Hospital,
Bristol,

BS10 5NB

Tel: 0117 323 5838 (Mon to Fri 09.00 – 17.00)

SECTION 8 – TRIAL INFRASTRUCTURE

8.1
Trial management group (TMG)

The TMG is responsible for the day-to-day management of the trial. The team is responsible for all aspects of the project (such as recruitment rate, budget management, protocol adherence, etc.) and for ensuring appropriate action is taken to safeguard trial participants and the quality of the study.

- Dr. Nick Maskell, Chief Investigator (CI) and principle investigator for Bristol.
- Dr. Rahul Bhatnagar, Trial Co-ordinator (TC) and a Clinical Research Fellow based at Southmead Hospital in Bristol
- Dr. Najib Rahman, Key investigator and principle investigator for Oxford.
- Miss Natalie Zahan, trial nurse in Bristol.
- The trial administrators will be based at the Respiratory Research Unit, based at Southmead Hospital in Bristol.
- Mr. Brennan Kahan, trial statistician

Identification of patients, insertion of IPCs and clinic-based follow-up will take place at the patient's local trial centre, by medical members of the trial team.

Routine drainage of patients' IPCs is to take place in the community. This will be performed by community nurses, lung cancer specialist nurses, or trial nurses, all of whom must be appropriately trained.

The Respiratory Research Unit at Southmead Hospital will have responsibility for authorisation, GCP and conduct, data integrity, data checking and database integrity.

Randomisation will be co-ordinated by Sealed Envelope (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA. Tel: 020 8959 9300).

8.2
Trial steering committee (TSC)

The TSC consists of both independent members as well as researchers working on the trial. The role of the TSC is to provide overall supervision of the study and monitor the progress of the trial to ensure that it is being conducted in accordance with the protocol, relevant regulations and the principles of GCP. The TSC will meet at regular intervals and will comprise:

Independent chair	Professor Robert Miller
Chief Investigator	Dr Nick Maskell
Trial Co-ordinator	Dr Rahul Bhatnagar
Key Investigator	Dr Najib Rahman
Trial Nurse	Miss Natalie Zahan

Trial Statistician	Mr Brennan Kahan
Thoracic Cancer Specialist Nurse Advisor	Miss Sarah Smith
Independent member	TBC
Patient representative	Mr Anthony Baxendale

8.3
Independent data monitoring committee (IDMC)

The IDMC is independent of the trial investigators. Its role is to review study safety data and provide advice to the TSC as to whether recruitment can continue.

Independent statistician	Ms Ly-Mee Yu
Independent physician	Professor Tim Peto
Independent physician	TBC

8.4
Recruiting Centres and Principal Investigators

Southmead Hospital, Bristol	Dr Nick Maskell
Bristol Royal Infirmary, Bristol	Dr James Walters
Churchill Hospital, Oxford	Dr Najib Rahman
Great Western Hospital, Swindon	Dr Andrew Stanton

SECTION 9 – ETHICAL ISSUES

9.1
Indwelling pleural catheters

Since the use of indwelling pleural catheters is considered to be standard practice in many centres around the world, there are no predicted ethical issues regarding their use as first-line management of malignant pleural effusions. Several studies have shown at least non-inferiority to the more established practice of traditional chest drainage and talc pleurodesis.

9.2
Talc

Talc, as used in the context proposed in this trial, is regarded as an Investigational Medicinal Product (IMP), and therefore the appropriate approval has been sought from the MHRA. No other new IMPs are to be used in the trial. There is no evidence that talc increases either morbidity or mortality in patients with malignant pleural effusions.

9.3
Consent and withdrawal

Consent for IPC insertion will occur to GMC standards, including a discussion of potential risks and alternative treatment strategies in every case. Written, informed consent for participation in the study will be obtained in every case, with adequate reflection time provided, and included information on risks and benefits of each procedure and the rationale for the study. Participants will give their permission for linked anonymous blood and pleural samples to be stored and analysed at North Bristol NHS Trust (NBT), or, if from Oxford, for those samples to be transferred to NBT for storage and analysis. Participants will be followed closely as described, and treated in line with standard local practices.

Patients will have the right to withdraw consent for any part of the study at any time, without giving any reasons for doing so. (See also Section 5.1)

9.4
Data security

Fully anonymised trial documentation will be securely stored for at least 5 years after study completion and thereafter disposed of according to regulatory requirements.

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APPENDIX 2 – Septation scoring

All ultrasound scans will be performed by experienced and fully trained operators of the research team. Scans will be used to assess the presence and degree of pleural fluid loculation, and maximum fluid depth.

To determine a septation score, an overall assessment of the degree of fluid septation and loculation should be made, with a score then being allocated as below. Following this, the site on ultrasound with the greatest degree of fluid septation and / or loculation should be selected, and a further score given for the degree septation and loculation in this specific area.

The overall septation score, **out of 6**, therefore consists of the sum of:

Assessment of the overall presence of septation and loculation

NONE	=	0
MILD	=	1
MODERATE	=	2
SEVERE	=	3

PLUS

Percentage of selected US field affected by septation and loculation

0 %	=	0
1-33 %	=	1
33-66%	=	2
66-100%	=	3

APPENDIX 3 – Abbreviations

°C	Degrees centigrade
AE	Adverse event
AR	Adverse reaction
CI	Chief investigator
CIOMS	Council for International Organization of Medical Sciences
CRF	Case report form
CT	Computed tomography
CXR	Chest x-ray
ECOG / WHO	Eastern Co-operative Oncology Group / World Health Organisation
EDTA	Ethylenediaminetetraacetic acid
EoT	End of trial
EQ-5D	EuroQol 5D health questionnaire
GMC	General Medical Council
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IPC	Indwelling pleural catheter
L	Litres
MDT	Multidisciplinary team
MHRA	The Medicines and Healthcare products Regulatory Agency
ml or **mls**	Millilitres
MPE	Malignant pleural effusion
NBT	North Bristol NHS Trust
NHS	National Health Service
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
PA	Posterior - Anterior
PI	Principal investigator
PSSRU	Personal Social Services Research Unit
QoL	Quality of life
SAE	Serious adverse event
SAR	Serious adverse reaction
SF-36	Short Form (36) health survey
SmPC	Summary of the product characteristics
SOB	Shortness of breath
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TC	Trial co-ordinator
TMG	Trial management group
TSC	Trial steering committee
VAS	Visual analogue scale

Section 1b – Final protocol

North Bristol NHS
NHS Trust

The efficacy of Indwelling Pleural Catheter placement versus IPC placement PLUS sclerosant (talc) in patients with malignant pleural effusions managed exclusively as out-patients

IPC + PLUS
TRIAL

Protocol

A single-blind, randomised controlled trial to determine the most effective method for management of malignant pleural effusions using indwelling pleural catheters.

Chief Investigator	**Professor Nick Maskell**
Trial Protocol Version	**6.0**
Version date	**09/09/2016**
R&I number	**2795**
REC	**12/SC/0242**
EudraCT Number	**2012-000599-40**
ISRCTN	**73255764**

Authorised by:

Name:	Prof Nick Maskell
Role:	Chief Investigator
Date:	9th September 2016

SIGNATURE

GENERAL INFORMATION

This document describes the IPC-PLUS trial and provides information about procedures for entering patients into it; the protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care was taken in its creation, but corrections or amendments may be necessary.

COMPLIANCE

The trial will be conducted in compliance with the protocol, Research Governance Framework, Data Protection Act and other guidelines as appropriate.

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Clinical queries should be directed to the local principal investigator, or to the trial co-ordinator or chief investigator

For general queries, supply of trial documentation and collection of data, please contact the trial administrator.

North Bristol NHS Trust is the main research Sponsor for this trial. For further information regarding the sponsorship conditions, please contact:

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FOR ENROLMENTS AND RANDOMISATIONS PLEASE CONTACT:

07972 411 835

(Monday to Friday 0830 to 1600)

If no answer call 0117 414 8114 or 07879 560856

CONTENTS

SECTION 1 – ABSTRACT AND TRIAL DESIGN

1.1
Abstract

Malignant pleural effusions remain a common problem with 40,000 new cases in the UK each year and up to 250,000 in the US [1]. They are increasing in incidence as survival rates of most cancers improve and life expectancy rises.

Controlling patients' symptoms of breathlessness by removal of the pleural fluid is the cornerstone of patient management, but these effusions will usually recur without more definitive intervention.

Traditional management of malignant pleural effusions has involved an inpatient stay with placement of a chest drain. This can then be followed by instillation of a pleural sclerosing agent such as talc, which aims to minimise further fluid build-up. Despite a good success rate in studies, this approach can be expensive, time-consuming and inconvenient for patients. More recently, an alternative method has become available in the form of indwelling pleural catheters which can be inserted and managed in an outpatient setting. They have also been shown to induce a pleurodesis in a small proportion of patients, but over a longer period of time.

Theoretically, therefore, the combination of indwelling pleural catheters and talc pleurodesis through this tube should provide the optimum management for malignant pleural effusions, with improved convenience for patients and a higher pleural symphysis rate.

We aim to prove, by way of a single-blind, multicentre randomised controlled trial, that this combination of treatments is superior to the use of indwelling pleural catheters alone. This study will recruit 154 patients and will assess the proportion of patients with successful pleurodesis at 5 weeks post randomisation. This study aims to help to define the future gold-standard out-patient management for patients with symptomatic malignant pleural effusions.

1.2
Lay summary

Many people with cancers (malignancies) can develop fluid in the space between the lung and the chest wall, known as the pleural space. This may be due to a tumour which directly affects the lung lining (the pleura), such as a mesothelioma, or another cancer from elsewhere which spreads to affect the pleura. If enough fluid accumulates the lung can be compressed, making patients feel significantly breathless. This fluid is termed a malignant pleural effusion.

The traditional method for dealing with this fluid is to admit the patient to hospital and insert a chest tube into the space around the lung where the fluid has built up. This allows

the fluid to be drained away in the first instance, alleviating symptoms. However, after the tube is removed, this fluid may build up again. This usually takes some time but can occur in only a few days. In order to try and prevent this re-accumulation, an irritant substance such as talc powder can be inserted through the chest tube. This aims to cause the two sides of the pleural space to stick together which obliterates the area in which fluid might build up. This is called pleurodesis. Whilst often relatively successful, this method of pleurodesis can be inconvenient for patients as they often need to be in hospital for at least 5 days.

In recent years an alternative method has become available. This involves the insertion of a chest tube, which is tunnelled under the skin, and hence can stay in place for much longer. Their main benefit is that they can be inserted as an outpatient and as more fluid builds up it can be tapped off, using the drain, as needed by community nurses. In the United States, these indwelling pleural catheters (IPC) are often the first line of treatment for malignant pleural effusions. Another benefit is that if left long enough, these tubes can also cause the pleural surfaces to adhere to each other and so may actually prevent further fluid build-up in much the same way as talc can. The rate of pleurodesis, however, is not as high as with talc, and if used for more than a few weeks the cost of using the IPC begins to exceed that of traditional treatment.

Our study aims to help determine the optimum management of patients with malignant pleural effusions by treating people with a combination of both indwelling pleural catheter and talc instillation. We shall compare the rates of pleurodesis at five weeks post randomisation, as well as patient reported outcomes and survival, with those treated with just a pleural catheter alone. In theory the addition of talc should improve time to pleurodesis, which would allow these catheters to be removed from patients more quickly. Although this study will look at patients from the UK, the results will be applicable globally and may help to change the way in which malignant pleural effusions are managed.

1.3
Study design

1.3.1
Trial type

Multi-centre, single-blind, randomised controlled trial to evaluate whether the combination of an indwelling pleural catheter and subsequent instillation of talc slurry is more effective at inducing pleurodesis than the use of an indwelling pleural catheter alone in the management of malignant pleural effusions in outpatients.

1.3.2
Disease / patients studied

The randomisation target is 154 participants. Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT) and through routine clinic appointments. Patients will be screened using the inclusion and exclusion criteria (see section 3.2 and 3.3). Eligible patients will be invited

to participate on a consecutive basis. Participation in the trial will be discussed with the patient at the appropriate routine outpatient appointment or consultation, and a patient information sheet given. Sufficient time, as determined by the patient, will be allowed to fully consider trial entry. Full written, informed consent will be obtained prior to enrolment.

1.3.3
Trial treatments

All patients will have an IPC inserted as per normal practice. Those eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant via the IPC (intervention group), or to receive a pleural placebo instillation of 0.9% sterile saline (control group).

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

Treatment allocation will be performed by Sealed Envelope Randomisation Services, an independent randomisation service. Minimisation with a random element will be used.

The minimisation factors are:

- Volume of pleural fluid removed in the first 10 days post IPC (≤1999 mls or ≥2000 mls)
- Malignancy subtype (Ovarian and breast; mesothelioma; other)
- Day 10 chest x-ray appearance (expanded with no evidence of trapped lung or evidence of trapped lung but fits the criteria for randomisation)

1.3.4
Outcome measures

Primary endpoint

2. The number of patients with successful pleurodesis at 5 weeks post randomisation, as defined by consecutive fluid volume measurement (see section 6.1.3).

Secondary endpoints

9. Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using
    a. EQ-5D health questionnaire
    b. QLQ-C30 health questionnaire
10. Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for
    a. Thoracic pain
    b. Breathlessness
11. Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation

12. All-cause mortality up to 10 weeks post randomisation.
13. Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
14. Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at two-weekly intervals for 10 follow-up period
15. Pleurodesis success at 10 weeks post randomisation, as defined by consecutive fluid volume measurement
16. Number of pleural procedures to relieve pleural fluid, excluding IPC drainage, from randomisation up to 10 weeks
17. Pleurodesis success at 5 and 10 weeks post randomisation, as defined by total volume of fluid collected over 2 consecutive weeks (see section 6.1.4)

1.3.5
Trial duration

Study follow-up will last until death or 10 weeks post randomisation, whichever is sooner. Patients will have an IPC inserted and will be randomised, if eligible, ten days later. They will then be reviewed at two weekly intervals. Patients will undergo IPC drainage in the community at least twice per week, with drainage volumes recorded at each occasion.

1.3.6
Investigational product

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. 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.

For the purposes of this trial, the intervention arm of the study will receive a talc slurry instillation ten days after IPC insertion, via the IPC. The slurry will consist of 4 grams of talc mixed with 50 mls of 0.9% saline. Those in the control arm will receive a placebo instillation of 50mls of 0.9% saline in lieu of talc slurry.

Intrapleural lidocaine of at a dose of 3mg/kg (to a maximum of 250mg) will also be given to patients in both arms.

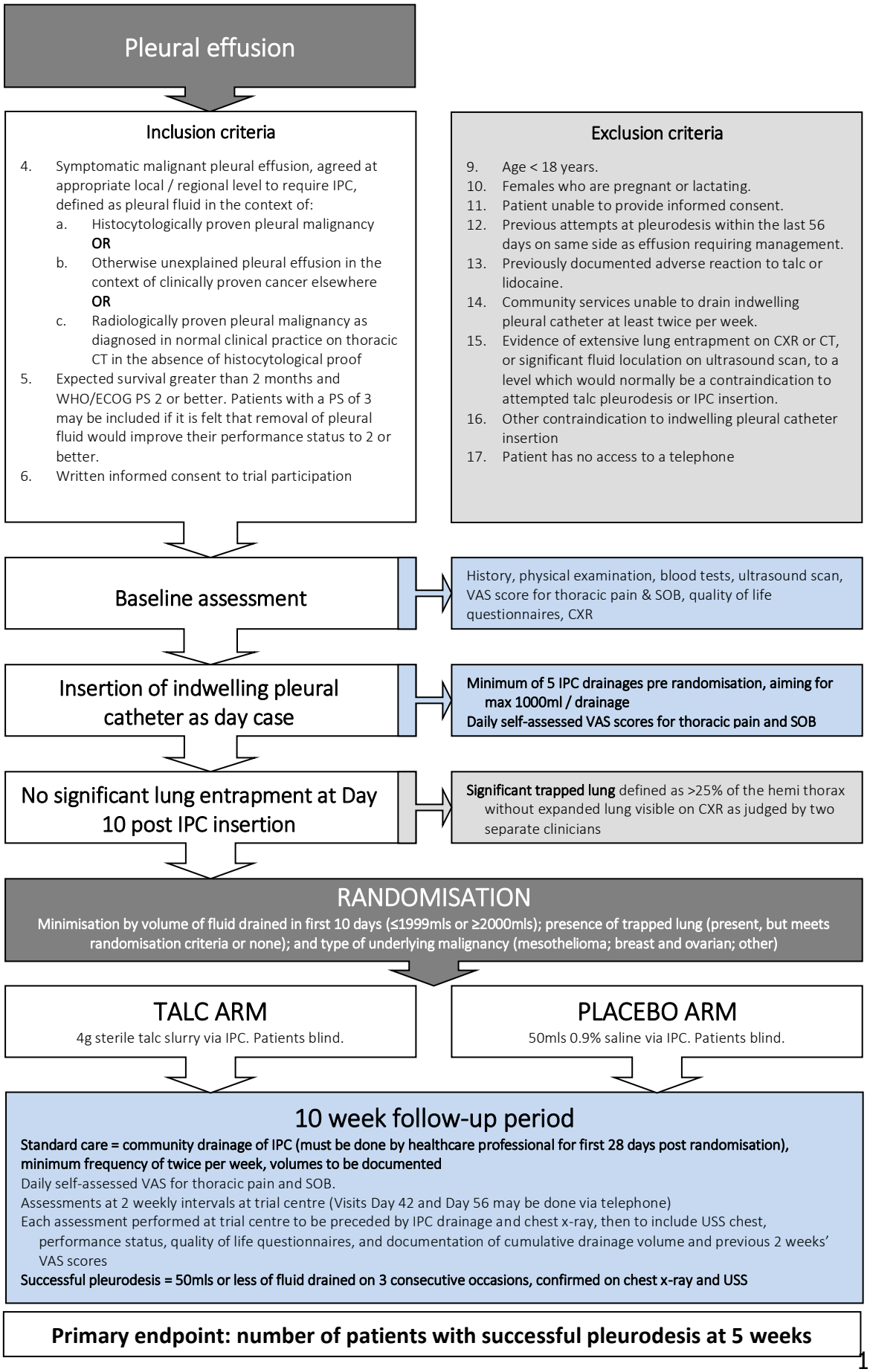
1.3.7
Trial centres

This trial will recruit from multiple hospitals, primarily NHS hospitals in the UK. All of the hospitals involved have dedicated pleural services and have a successful track record of recruiting to pleural clinical trials. The lead centre will be North Bristol and the trial will be co-ordinated by a clinical research fellow based there, who will be responsible for trial setup, delivery, liaison and query resolution at the other sites.

1.3.8
Trial sponsor

The study is sponsored by North Bristol NHS Trust, who will oversee and ensure the compliance and integrity of the trial.

1.4
Trial flowchart



SECTION 2 - BACKGROUND

2.1
Scientific summary

Malignant pleural effusions (MPE) are a common complication of many cancers. Their presence usually indicates metastatic disease, and hence possibly a poorer prognosis. The majority of cases are due to lung cancer in men and breast cancer in women [2], although many other malignant processes can lead to fluid developing, including primary pleural disease such as mesothelioma or more generalised processes such as lymphoma [3].
In order for an effusion to be formally defined as malignant, there should be direct histological or cytological evidence of tumour in either the pleura or the fluid itself. However, the mean sensitivity of cytological examination is around 60% [4] and pleural biopsy is not always possible. Histology from the primary tumour, in combination with fluid biochemistry, is also therefore often used to make the diagnosis.

Since the primary malignant source of these effusions can be varied, it can be difficult to reliably predict survival based on their presence alone. Median survival has approached 2 years in some series [5] but the typical figure is generally lower at 4 to 12 months [6,7]. Patients with a hormone sensitive tumour, such as breast cancer, tend to have a better outcome.

The rate of fluid production may be determined by many factors, including underlying tumour type, but these are not yet well understood. Local audit data has suggested that serum levels of NT-ProBNP may have a predictive role in fluid volumes, and could therefore be used to guide patients' treatment. NT-ProBNP is a polypeptide which is secreted alongside BNP (brain natriuretic peptide) in response to pathological myocardial stretch. It has been shown to be of value as a negatively predictive test for the presence of heart failure [8] and has become more widely used by community medical services.

The traditional management of malignant effusions involves inpatient insertion of a chest drain, to ensure fluid drainage and pleural apposition, before the instillation of a sclerosant substance to cause pleural inflammation and adhesion. This aims to obliterate the pleural space and thus fluid build-up, and is known as chemical pleurodesis. Many substances can be used as a pleural irritant although by far the most commonly used is talc, which has been shown to be superior to alternatives such as tetracycline or bleomycin [9].

Talc is predominantly hydrated magnesium silicate and has been used for the purposes of pleurodesis since the 1930s [10]. For many years ungraded talc was used but this was associated with instances of severe inflammatory response, both systemically and locally [11, 12], which were later confirmed experimentally. Subsequent evidence has however shown that graded large-particle, sterile talc can be both safe and effective if used in doses up to 4 grams [13], and this is now the standard for chemical pleurodesis across much of the United Kingdom. It may be instilled using a chest drain in the form of a slurry, or can be sprayed thoracoscopically under direct vision. The thoracoscopic approach was not shown to be superior in a Cochrane review [9] and this was backed up by a recent large US-based RCT [14].

Pleurodesis success rates quoted in studies are typically high with talc, ranging from 81% to 100% [15], although these figures may vary considerably in real-world practice due to differences between clinicians and individual centres. To achieve such efficacy a patient is typically admitted for insertion of a chest tube and drainage. Only once the pleural space is felt to be dry is talc inserted. This usually requires an inpatient stay of 5-7 days [16], often with at least 24 hours of pleural suction, and has significant health economic impact as well as the potential to impair the quality of life of patients with more limited life spans. Following the widespread use of large-particle talc, the side effects of pleurodesis have tended to be minor, the commonest being fever, pain and gastrointestinal upset [9,17,18], although there have been rare cases of empyema [19]. For this reason the routine use of sterile technique and analgesia is recommended when pleurodesis is attempted, including premedication with intrapleural lidocaine [15]. It should also be noted that, in those with malignant pleural effusions, there has been no documented increase in mortality by the use of talc pleurodesis over the use of either alternative agents or chest drains alone [9].

The main drawback of the traditional method of pleurodesis is the length of hospital stay and the inconvenience to patients. In more recent years, the use of indwelling pleural catheters has become more widespread and has brought the potential to alleviate these problems.

Indwelling pleural catheters (IPC) are silastic tubes, which have the potential to be left in place for weeks to months after being tunnelled under the skin. They can be inserted, with the appropriate training, under local anaesthetic or at thoracoscopy, and can even be performed as a day-case [20]. Once at home, the aim is to drain fluid regularly (usually three times per week) in the patient's own environment. This maximises the opportunity for pleural apposition and adhesion which potentially leads to complete pleurodesis – the presence of foreign material in the pleural space contributes to this. Drainage can be performed by anyone with appropriate training – the patient included – but is often managed by district nursing teams.

IPCs have been shown to be effective in the management of malignant pleural effusions, although there is a paucity of evidence comparing them directly to talc pleurodesis. In a retrospective series of 250 cases, almost 90% of patients experienced complete or partial relief of dyspnoea [21], a finding bettered in a later study in which all patients experienced improvement [22]. A recent meta-analysis has confirmed an overall 96% symptom improvement rate [23]. Indwelling drains have also been shown to improve more formal quality of life scores, even in comparison to talc pleurodesis [24]. Length of hospital stay can be significantly reduced when compared to traditional methods, one study demonstrating a five-day reduction in average inpatient time in the IPC group [25]. Despite the need for proprietary drainage kits they can also be cheaper overall to healthcare providers if used for less than 6 weeks [26]. This is an achievable goal as IPCs can often be removed following cessation of drainable fluid, a reliable surrogate indicator for pleurodesis. Such spontaneous pleurodesis generally occurs in around 50% of cases [21,22,27] and is heavily influenced by the underlying tumour type [28], although rates as high as 70% were reported in one study [29]. This group, however, had a mean time to pleurodesis of 90 days; the typical length of time to achieving pleural fusion commonly being quoted as one to two months [21,28]. The presence of 'trapped lung' (visceral pleural scarring) can lead to incomplete expansion following

drainage, and may be an indication for insertion of an indwelling pleural catheter, which no doubt influences the variability of the time to pleurodesis in these studies. In patients with these conditions, the failure of pleural apposition makes pleurodesis extremely unlikely as an enlarged pleural space persists even with drainage.

Pleural pressure measurement has been available for many years and can help in determining if there is likely to be abnormal lung expansion. Normal pressures can be difficult to determine but they are felt to represent a balance between the elastic recoil of the lung and the tendency of the chest wall to expand, with values typically being quoted as slightly sub-atmospheric (-3 to -5 cmH_20) [30].

During measurement, the manometer should be placed at the most dependent part of the fluid as this allows the maximum volume of fluid to be removed, and ensures the minimum contact between the lung and the catheter, which in turn ensures that the pressure in the pleural space is recorded accurately [31].

Previous studies have analysed the changes in both pleural pressure and pleural elastance (change in pressure divided by the change in volume), and have suggested typical patterns for lungs with normal recoil properties; those with lung entrapment; and those with trapped lung. Patients with trapped lung will tend to have a low or negative initial pressure, which then drops off sharply. Entrapped lungs may have a normal initial curve followed by a sharp pressure drop as fluid is removed. Normal lungs should exhibit only minimal pressure change as fluid is removed, with values approaching normal towards the end of the drainage [32].

A study by Lan et al. looked at pleural elastance during thoracentesis, to act as a surrogate for lung expansion. They found that an elastance of at least 19 cmH_20 after removal of 500mls of fluid predicted lung entrapment and therefore pleurodesis failure[33]. This situation is felt to be ideal for the use of IPCs as recurrent fluid accumulation is much more likely.

Indwelling pleural catheters are not without drawbacks however. There may be significant pain associated with the immediate and short-term post procedure period, and in some cases pleural tract metastases have been documented, although this has rarely exceeded 3% [34] and is usually under 1% [23]. In addition, their insertion requires specific training, which still does not guarantee success – a failure rate of 4% was documented in the largest series to date. This same group reported other complications including empyema formation (3%); secondary fluid loculation (12%), and cellulitis (2%) [21]. Nevertheless, meta-analysis data has shown IPCs are generally safe to use, with an overall complication rate of 12.5% [23].

It would seem, therefore, that the optimal approach to the management of malignant pleural effusions should be the combination of talc instillation, to achieve the highest pleurodesis rates, and placement of an indwelling pleural catheter to allow greater convenience and quality of life for the patient, and potentially lower healthcare costs. Despite the potential for combining these methods having been recognised [35] there have been no studies to date to test this hypothesis, although ambulatory pleurodesis for malignant effusions was attempted in one small series by Saffran et al [36]. A closed-system pigtail catheter was inserted and pleurodesis was attempted at a later date using 4 grams of

talc. Patients were managed as outpatients and the authors describe their method as being a viable alternative to traditional inpatient management. However, patient numbers were limited to 10 and there was no attempt at randomisation. The study took place before the widespread introduction of IPCs.

The IPC-PLUS trial aims to test the hypothesis that the combination of an IPC plus talc sclerosant is superior to an IPC alone in the management of malignant pleural effusions. This trial has the potential to significantly affect the way in which such effusions are managed in the future, on a global scale.

2.2
Research questions

2.2.1
Primary research question

In patients with a proven malignant pleural effusion;

2. Does the use of talc as a sclerosant in conjunction with an indwelling pleural catheter (IPC) increase the number of patients achieving successful pleurodesis, when compared to using an IPC alone?

2.2.2
Secondary research questions

9. Does using talc and an IPC together alter the amount of pain and breathlessness a patient experiences, when compared to using an IPC alone?

10. Does the use of talc and an IPC together alter a patient's quality of life, when compared to using an IPC alone?

11. What are the medical complications of using talc in conjunction with an IPC?

12. What are the logistical and clinical difficulties with using talc in conjunction with an IPC?

13. Does the combination of talc and an IPC together influence the degree of fluid septation and loculation seen on thoracic ultrasound?

14. Does the baseline level of serum brain natriuretic peptide (BNP) correlate with the volume of pleural fluid drained and chance of successful pleurodesis?

15. Does pleural elastance during initial drainage correlate with lung entrapment and the chance of successful pleurodesis?

16. Is using talc in combination with IPC cost-effective when compared to IPC alone?

SECTION 3 – PATIENT SELECTION

3.1
Setting

Patients will be recruited from multiple trial centres in the UK. The trial is supported by the appropriate local and regional cancer networks.

Clinical care, drain insertion and imaging will be provided by local medical professionals at the patients' base hospitals, 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. All drainages up to the day 28 post randomisation visit will be performed by appropriately trained medical staff such as district nurses, lung cancer specialist nurses, or research nurses. After this, drainages may be performed by anyone who has been appropriately trained (except the patient themselves). The specifics of follow-up are detailed in section 4.2.3.

3.2
Inclusion criteria

4. Symptomatic malignant pleural effusion, agreed at appropriate local / regional level to require an IPC, defined as pleural fluid in the context of;
    a. Histocytologically proven pleural malignancy
    OR
    b. Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere
    OR
    c. Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof

5. Expected survival greater than 2 months and WHO/ECOG performance status of 2 or better. Patients with a PS of 3 may be included if it is felt that removal of pleural fluid would improve their performance status to 2 or better.
6. Written informed consent to trial participation.

3.3
Exclusion criteria

9. Age < 18 years.
10. Females who are pregnant or lactating.
11. Patient unable to provide informed consent.
12. Previous attempts at pleurodesis within the last 56 days on same side as effusion requiring management.
13. Previously documented adverse reaction to talc or lidocaine.
14. Community services unable to drain indwelling pleural catheter at least twice per week.

15. 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.
16. Other contraindication to indwelling pleural catheter insertion
17. Patient has no access to a telephone

3.4
Recruitment

The randomisation target is 154 patients. The statistical justification for this is given in section 6.2. Patients with malignant pleural effusions will be identified following early discussion at each centre's cancer multidisciplinary team meetings (MDT), through routine clinic appointments, and through inpatient reviews. It is expected that the local thoracic MDTs and clinics, and regional mesothelioma MDTs will provide the highest number of patients. Patients will be screened using the inclusion / exclusion criteria as above. Screening logs documenting reasons for exclusions will be kept throughout the trial.

Eligible patients will be invited to participate on a consecutive basis, and will be provided with an information leaflet at the earliest opportunity. Participation in the trial will be discussed with the patient at the appropriate outpatient appointment or consultation, which will form part of their normal care pathway. They will be allowed sufficient time, as determined by the patient, to fully consider trial entry, as well as to ask questions of investigators. Full written, informed consent will be obtained prior to enrolment.

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

3.5
Co-enrolment guidelines

For the duration of a patient's involvement with IPC-PLUS data collection, they should not be entered into any other clinical trial which attempts to directly affect pleural fluid production, management or drainage. Oncological management of the underlying disease will be guided by the site-specific cancer MDTs, and any treatments or entry into relevant systemic anti-cancer trials will not be restricted. Should a participant be considered for co-enrolment in another trial of any origin then liaison with the IPC-PLUS trial team is essential to ensure compatibility between the trial protocols.

Once a patient has had their drain removed any further management, including the repeat use of IPC, will be at the discretion of local clinicians. However, patients may only be randomised into the IPC-PLUS trial once.

SECTION 4 – ASSESSMENT AND TREATMENT OF PATIENTS

4.1
Standard care

All patients should have been discussed in their local thoracic MDT, or, if the underlying malignancy is not pulmonary, an appropriate specialist MDT. Mesothelioma patients should be discussed at a regional MDT if available. Patients should have been referred to their local oncologist for discussion and consideration of their treatment options in the usual manner. For all issues other than those pertaining to the drainage of the malignant pleural effusion, treatment discretion lies with the primary physician, surgeon or team.

Normal clinical review will take place in the usual oncology or respiratory clinic. The frequency of clinical review will depend on patient choice, severity of symptoms and clinical discretion. In general, patients who are managed with chemotherapy for underlying malignancy are reviewed every 2-3 months.

All attempts should be made to co-ordinate trial follow-up and routine follow-up appointments. Patients should be given contact details for an appropriate specialist nurse at the earliest opportunity.

Patients will usually be offered placement of an indwelling pleural catheter by a respiratory team, radiologist or surgeon.

4.2
Trial interventions

4.2.1
Pre-randomisation

Interventions and procedures to be performed during the pre-randomisation period are summarised in appendix 3.

Potential patients will be screened as described above. Those who may be suitable for an IPC will have this option discussed in a normal outpatient or inpatient setting, where they will also be given the option of participating in the IPC-PLUS trial. A written information sheet should be provided to those who are initially eligible and willing to be entered. Sufficient time, as determined by the patient, will then be given to consider the information provided and to decide whether they wish to participate in the trial. Sufficient time will also be allowed for questions and answers prior to written, informed consent being taken.

Prior to consent being taken, the patient should undergo a routine thoracic USS looking for evidence of significant loculation to ensure IPC insertion, and trial entry, are still appropriate.

Consent for trial entry must be taken by a member of the trial team and should take place before the placement of the patient's IPC. The most convenient opportunity may be at the same time as consent is taken for the IPC insertion.

Once an eligible patient is consented, a unique trial identifier will be allocated according to the appropriate SOP. A baseline assessment will then be undertaken by a member of the trial team and entered onto the appropriate Case Report Form (CRF). Much of this information may already be available from recent consultations and will include:

- Relevant medical history and physical examination, to include;
    - Onset and nature of symptoms
    - Type of malignancy causing effusion (if known)
    - Pleural procedures to date
    - Current ECOG / WHO performance status
    - Current analgesia history
    - Current and projected treatment plan outside of IPC-PLUS
- Results of standard blood tests (from within 10 days prior to IPC insertion)
- Visual-Analogue Scale (VAS) score to assess thoracic pain and breathlessness
- Quality of life assessment using EQ-5D and QLQ-C30 health questionnaires
- Chest x-ray, ideally PA (from within 24 hours)
- Thoracic ultrasound scan

At the recruitment sites in North Bristol and Oxford, along with the standard blood tests, additional 'trial blood samples' should be taken for centrifuge and storage, to allow for cytokine analysis at a later date. Details of samples to be taken are given in section 4.2.8. An SOP for sample processing will be provided where needed.

Patients will then be given an appointment, if this has not already been provided, to have an indwelling pleural catheter inserted as a day case procedure. This should be within one week of the baseline assessment. If an appointment cannot be made within this time, this should be recorded as a protocol deviation.

IPCs must be placed by an appropriately trained member of staff, but not necessarily a member of the trial team. The IPC insertion CRF should be completed during or immediately after the procedure. Immediately following drain placement, a therapeutic aspiration 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. During drainage, wherever possible, patients should have pleural pressures measured using a calibrated pleural manometer, after every 100-200 mls removed (see manometry SOP). These recordings should be entered onto the case report form (CRF) and the total volume removed recorded in the patient's drainage booklet. Fluid samples should only be collected from the North Bristol and Oxford sites as detailed in section 4.2.8.

A chest x-ray should be performed post-procedure to confirm adequate drain placement.

Prior to discharge, the patient will be issued with a drainage booklet which will act as a record for the volumes of fluid drained throughout their period of trial participation. They will also be given a chart on which they can complete their own VAS scores for pain and breathlessness, which should be done on a daily basis. They should be given an appointment for follow-up in 10 days. If convenient follow-up cannot be arranged for day 10 then the patient may be given an appointment for within 24 hours of day 10 (either before or after). Any appointments falling outside of this 72 hour window should be detailed as a protocol deviation.

For the period post IPC insertion and before their randomisation visit, patients should have their fluid drained on at least 5 occasions, the initial drainage being immediately after IPC insertion prior to discharge. This first drainage may be to the maximum clinically appropriate volume. Subsequent drainages, to maximum of 1000mls per drainage, will ideally be performed in the community by appropriately trained healthcare professionals such as district nurses, research nurses or lung cancer specialist nurses, however drainages may be performed at the local trial centre if necessary. After each drainage the volume removed should be recorded by the person removing the fluid. The patient's fifth drainage can take place as part of their randomisation visit on day 10.

Patients will attend their local trial centre 10 days (+/- 1 day) after IPC insertion. Their catheter should be drained to dryness, or as close to dryness as allowed by symptoms (patients should remain well enough to undergo randomisation after this procedure). 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. Quality of life will be assessed using the EQ-5D and QLQ-C30. 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 one third of the hemi thorax as judged by two separate clinicians using visual estimation on chest x-ray), then the patient should be excluded from randomisation. 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. Patients who do not meet the criteria for randomisation should have their on-going care devolved to the appropriate local services. Patients may also be excluded for other clinical reasons not relating to the degree of lung entrapment or residual fluid. Such patients should have the details of their exclusion outlined on the appropriate CRF and may be discussed with the CI if needed.

If a patient is eligible for trial entry at this point then they should be randomised at the same visit and given the allocated instillation substance before returning home.

4.2.2
Randomisation

Interventions and procedures to be performed during the randomisation and post randomisation periods are summarised in appendix 3.

Those eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant via the IPC, or to receive a pleural placebo instillation of 0.9% sterile saline. Treatment allocation will be performed by Sealed Envelope Randomisation Services (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA), an independent randomisation service. Minimisation with a random component will be used.

The minimisation factors are:

- Volume of pleural fluid removed in the first 10 days post IPC (≤1999 mls; ≥2000 mls)
- Malignancy subtype (Ovarian and breast; mesothelioma; other)
- Day 10 chest x-ray appearance (expanded with no evidence of trapped lung; evidence of trapped lung but fits the criteria for randomisation)

A member of the research team will contact the randomisation service as soon as both lung entrapment and residual fluid are excluded.

4.2.3
Post-randomisation (instillate allocation and administration)

The allocated treatment substance must not be communicated to the patient. The procedure for the instillation of the allocated substance should remain the same for both groups, and is outlined in the appropriate standard operating procedure (SOP). Patients must be kept blind from the substance they are receiving by concealing the syringe; by preparing the instillate in a separate room; and by administering the allocated substance from behind the patient, with the patient facing forward. All instillations should be followed by an adequate flush to ensure as little as possible of the allocated substance is left in the IPC line.

Patients will then be provided with a further self-assessment VAS sheet to encompass the next 14 days, and instructions should be given for this to be completed on a daily basis at the same time each day. They will also be given an appointment card which will outline the schedule for their follow-up period. This should be completed with details of their next appointment at each consultation prior to discharge. All patients will be issued with a standard minimum amount of analgesia to take home, as outlined in the SOP.

4.2.4
Community drainage

Following randomisation and the allocated instillation, all patients should receive fluid drainage in the community, although if necessary patients may attend their local trial centre. This will be done by an appropriately trained healthcare professional up to and including the day 28 follow-up visit. After this, until the end of the trial follow-up period,

drainages may be performed by anyone with an appropriate level of training. This may include the patient's family or carers, but should not be the patient themselves. The frequency of drainage will be at the discretion of the patient and community team but should occur **at least twice per week**, and should begin at three times per week.

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

Patients will have been provided with a self-assessment VAS booklet for thoracic pain and breathlessness. This will cover the time period between outpatient visits and should be completed at the same time each day, ideally before a drainage takes place. Patients should bring this booklet, along with their drainage booklet, to each clinical assessment.

4.2.5
Clinical assessments (DAYS 14, 28, 42, 56, 70)

The follow-up period for each patient is 10 weeks post randomisation, or until death.

During this time, the first clinical assessment will occur 14 days after randomisation, and at two-weekly intervals thereafter. All follow-up appointments should ideally take place in the patient's base hospital or in an appropriate satellite centre. However, if necessary, the appointments scheduled for days 42 and 56 may take place over the telephone. Appointments on days 14, 28 and 70 must take place at the base hospital or satellite centre. In the event that an assessment cannot be performed on the allocated day, an appointment or follow-up telephone call should be arranged for within 24 hours (before or after) of the originally planned day, and the change documented on the appropriate CRF. If the patient cannot be assessed within this 72 hour window then another appointment should be made for as soon as possible, and the delay reported on a protocol deviation form.

4.2.6
Face-to-face appointments (Mandatory on days 14, 28 and 70, optional on days 42 and 56)

Before the assessment, but following arrival at the hospital, the IPC should be drained to dryness by a trained member of staff, with pleural fluid samples stored at appropriate centres as detailed below. The assessment should then be completed on 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 IPC placement through history and examination
- Documentation of analgesia requirements (DAY 14 only)
- Documentation of chemotherapy / radiotherapy and any response
- Current ECOG / WHO performance status
- Quality of life assessments using EQ-5D and QLQ-C30 health questionnaires

At each visit, patients should also have a chest x-ray (ideally PA) and undergo a thoracic ultrasound, completing the ultrasound CRF alongside.

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

4.2.7
Telephone appointments (Optional on days 42 and 56)

Any appointment which is to be performed over the telephone should consist of the following:

- A verbal reminder to the patient to complete and send their quality of life questionnaires and VAS booklets back to their local trial centre, ensuring that a VAS score is completed during the telephone consultation.
- Completion of a specific telephone follow-up CRF by the researcher, along with the standard health service use CRF
- A review of drainage volumes with the patient over the telephone
    - If drainage volumes appear to have reduced to a level suggesting pleurodesis, or if there is any suspicion of a drainage or IPC complication, then the patient must attend for the next scheduled follow-up visit. Alternatively, a patient may attend the following day for a full face-to-face visit with the telephone follow-up being discarded

4.2.8
Removal of drains

Once inserted, drains 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 may include local subcutaneous or pleural infection, intolerable pain, significant fluid loculation, or cessation of fluid drainage.

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.

Any patient who has a drain removed during their trial period will continue to undergo planned follow-up for the full 70-days.

4.2.9
Blockage of drains

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, perhaps due to cessation of drainage with persistent chest x-ray or ultrasound changes, then standard local unblocking procedures should be followed. This may involve a short hospital admission for administration of intrapleural urokinase. 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.

4.2.10
Biological samples and storage

During the pre-IPC baseline assessment, all patients should have standard blood tests for full blood count, urea and electrolytes, liver function, clotting function and C-reactive protein taken if there are no results available for within the previous 10 days. In addition to these, at the research sites at North Bristol and Oxford, 1 EDTA, 1 serum gel tube, and 1 citrate tube of blood should be taken. Shortly after, during IPC insertion, 1 EDTA, 1 serum gel tube, and 1 citrate sample tube of pleural fluid should also be collected from patients at the North Bristol and Oxford sites. All such trial samples should be processed as per the appropriate SOP before being frozen and stored.

At the North Bristol and Oxford research sites, prior to each trial follow-up appointment (every two weeks for 10 weeks), additional samples of pleural fluid should be collected during IPC drainage and processed in the same manner as above.

Participants will give their permission for linked anonymous blood and pleural samples to be stored and analysed at North Bristol NHS Trust (NBT), or, if from another site, for those samples to be transferred to NBT for storage and analysis. Samples will be stored in a dedicated Respiratory Research Unit freezer in the University of Bristol laboratory on the NBT site. Samples will be stored, anonymised and eventually destroyed in line with local policy

4.2.11
Ultrasound scans

All ultrasound scans will be performed by experienced and fully trained operators of the research team. Scans will be used to assess the presence and degree of pleural fluid complexity, and fluid depth (standard practice). These parameters will be recorded on the ultrasound CRF.

4.2.12
Visual Analogue Scale (VAS) scoring

VAS scores will be collected for each patient, beginning at their baseline assessment and ending when their follow-up is completed or is terminated due to death, withdrawal or ineligibility to undergo randomisation.

All patients will complete a VAS score for thoracic pain and breathlessness during their baseline assessment. After IPC insertion, beginning the following morning, patients should repeat these scores using the documentation provided. Similar VAS scores should be recorded on a daily basis for the duration of trial involvement, with recordings being made

each morning. If IPC drainage is due to take place that day, then the score should be noted before the drainage takes place.

Patients will be provided with a chart which allows them to record VAS scores for 2 weeks. Completed charts should be brought to each trial follow-up assessment and will be replaced as needed. If a patient dies before all charts can be collected, these should be sent via mail to the local trial centre.

4.2.13
End of trial

The trial will cease recruitment once the target of 154 randomised patients has been met. The provisional end of trial (EoT) date will therefore be 10 weeks after the randomisation of the 154th trial patient. 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. This will require consent to be given separate to trial involvement.

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

4.2.14
Investigational product

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. 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 ten 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. Those in the control arm will receive a placebo instillation of 50mls of Sodium Chloride (0.9% w/v Intravenous Infusion BP) in lieu of talc slurry, which is licenced as a vehicle for drug administration and can be administered intrapleurally. No adverse effects due to the use of 0.9% saline are anticipated.

SECTION 5 – PATIENT WITHDRAWAL AND FOLLOW-UP COMPLICATIONS

5.1
Patient withdrawal

Patients will have originally consented to trial follow-up, and to sample collection, storage and analysis where appropriate. Patients 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 patient's CRF, and clarification on the nature of the withdrawal of consent, as outlined below, should be sought. Patients may still be stratified as 'alive' or 'dead' at the end of their follow-up period, unless consent for clinical data use is withdrawn. Patients who withdraw before randomisation will not be included in the final analysis.

5.1.1
Withdrawal of consent to all trial involvement

The patient 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.

5.1.2
Withdrawal of consent to follow-up and further clinical data collection only

The patient 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.

5.1.3
Withdrawal of consent to follow-up, further clinical data collection, and clinical data use
The patient withdraws consent to further follow-up visits, recording of clinical data, and the use of any clinical data already collected in analyses.
They maintain consent for blood and fluid samples already taken to be analysed.

5.1.4
Withdrawal of consent to sample analysis only
The patient withdraws consent for their previously taken blood and pleural samples to be analysed, or for any data already obtained from such samples to be used in the final analysis. Samples and associated data should be destroyed in line with local policy. They maintain consent for trial follow-up, clinical data collection and the use of this data in the final analysis.

5.2
Other follow-up complications

If a patient moves to another area outside the trial catchment, every effort should be made to continue follow-up in conjunction with the new local services, or via the new GP.

SECTION 6 – STATISTICAL CONSIDERATIONS

6.1
Outcome Measures

6.1.1
Primary endpoint

2. The number of patients with successful pleurodesis at 5 weeks post randomisation, as defined by consecutive fluid volume measurement (see section 6.1.3).

6.1.2
Secondary endpoints

9. Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using
    a. EQ-5D health questionnaire
    b. QLQ-C30 health questionnaire
10. Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for
    a. Thoracic pain
    b. Breathlessness
11. Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
12. All-cause mortality up to 10 weeks post randomisation.
13. Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
14. Degree of loculation of pleural fluid following talc instillation as judged by thoracic ultrasound and septation score at two-weekly intervals for 10 follow-up period
15. Pleurodesis success at 10 weeks post randomisation, as defined by consecutive fluid volume measurement
16. Number of pleural procedures to relieve pleural fluid, excluding IPC drainage, from randomisation up to 10 weeks
17. Pleurodesis success at 5 and 10 weeks post randomisation, as defined by total volume of fluid collected over 2 consecutive weeks (see section 6.1.4)

6.1.3
Successful pleurodesis by measurement of consecutive drainages (Primary endpoint)

For the primary outcome measure, successful 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, who should be blind to treatment allocation. Information on drainage volumes will be collected in the community and during follow-up visits as described above. The x-ray for chest opacification must have been taken after the third consecutive occasion of collection less than 50mls, and within the 10 week follow-up period. All three occasions of collection less than 50mls should also occur within the 10 week follow-up period.

Patients who drain less than 50mls of fluid on three or more occasions but who continue to have greater than 25% pleural opacification on chest x-ray due to pleural fluid (as proven by thoracic ultrasound), will be defined as having an unsuccessful pleurodesis. If there is a clinical suspicion that the drain may be blocked then appropriate attempts to resolve this should be made prior to a definition being made.

The achievement of pleurodesis should be dated to the first drainage of less than or equal to 50mls. Even if patients achieve the requirements for pleurodesis during the trial period, they will continue to receive fortnightly follow-up as originally planned until the 70-day follow-up period is complete.

Patients who die during the 10-week trial period will be assessed for whether they achieved pleurodesis success prior to death. This requires 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, who should be blind to treatment allocation, with the x-ray having been taken after the third consecutive collection volume of less than 50mls.

6.1.4
Successful pleurodesis by measurement of total volume over time (Secondary endpoint)

As part of a secondary analysis, patients who have recorded drainages of less than or equal to a total of 250mls of fluid over two consecutive weeks during their follow-up period (with appropriate radiological findings) will also be defined as having a successful pleurodesis. The period of two consecutive weeks may begin with any drainage which is undertaken during the post-randomisation trial period, and ends two weeks later on the same day of the week. The drainage volume recorded on this final day is included in the total volume for the two week period. Patients must be drained no less frequently than twice per week.

In order to be defined as having a successful pleurodesis, a patient's chest x-ray must have chest opacification on the side of the IPC of less than 25%, as judged by 2 independent clinicians, who should be blind to treatment allocation. The x-ray for chest opacification must have been taken after the 2-week period's last drainage, and within the overall 10 week follow-up period.

For patients who successfully drain less than or equal to 250mls of fluid in a two week period, the date of pleurodesis is defined as the day of the first drainage in that period. All drainages which count towards the total volume must occur within the study period.

Patients who die during the follow-up period will also be assessed for pleurodesis using measurements collected prior to death. The clinical and radiological parameters used to define successful pleurodesis by volume over time remain the same as those described above.

6.1.5
Other outcome measures

3. Association between baseline levels of serum NT-ProBNP and pleurodesis success
4. Association between pleural elastance during initial fluid drainage and pleurodesis success

6.2
Sample size

Talc pleurodesis alone has been shown to be up to 90% efficacious in trial conditions [15], and we expect the combination of talc and IPC to be at least as effective as talc alone. IPCs used alone have a more variable range for pleurodesis efficacy but it is thought to be around 50% [21,22,27] for pulmonary or pleural malignancies, which are expected to make up the bulk of our trial cases.

In order to detect a 25% difference in pleurodesis success at 5 weeks (60% IPC alone vs 85% IPC and talc) with 90% power, a 5% significance level, and 5% loss to follow-up, we would require 154 patients (77 in each arm).

Based on current audit data, we expect each primary trial centre to see more than 8 potentially eligible patients per month. Therefore, assuming a consent rate of 35-50%, recruitment would take between 13 and 18 months.

6.3
Statistical analysis

The primary analysis will be by intention-to-treat, and will include all randomised patients on whom an outcome is available. All tests will be two-sided, and all analyses will be adjusted for the minimisation variables. The primary outcome will be analysed using a time-to-event regression model, which will include mortality as a competing risk.

A full statistical analysis plan will be written prior to data unblinding. This is considered version 0.1 of the analysis plan.

6.4
Interim analysis

The Independent Data Monitoring Committee (IDMC) will review the trial at regular intervals to assess patient safety. No additional interim analyses to evaluate efficacy are planned.

6.5
Health economic outcomes

The perspective adopted in the economic analysis will be that of the English National Health Service and Social Services. As a result we will collect information on the following resource use items:

3. *Intervention costs*. This will entail collecting information on talc, consumables and staff time. This information will be obtained by reviewing hospital records. Should a significant between-group difference in the rates of IPC blockage and drain removal occur, these will also be included in the intervention cost analysis.

4. *Follow-up costs*. This will entail collecting information on patients' use of hospital resources after randomisation. Information collected will include: inpatient stays, outpatient services, use of emergency departments and ambulance costs. Information on inpatient stays will be obtained by reviewing the administrative care records in each of the participating centres.

Resource use items will be priced using unit cost schedules and salary scales such as PSSRU, NHS Trust Financial Returns and NHS Reference costs. If necessary, finance departments at each of the study centres will be contacted to obtain unit cost information not included in these sources.

As the main outcome measure in the economic evaluation will be incremental cost per Quality-Adjusted Life Year (QALY) gained, generic quality of life information will be collected using the the EuroQol EQ-5D – a widely used generic multi-attribute utility scale. This will be completed for each patient at baseline and at each hospital assessment (randomisation, and at days 14, 28, 42, 56 and 70 post-randomisation) to measure patients' general health related quality of life. For QALY construction, EQ-5D results will be translated into utility values using published UK population valuations.

SECTION 7 – ADVERSE EVENTS

7.1
Definitions

Adverse Event (AE): any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP), whether or not considered related to the IMP.

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered. All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the SmPC which occur in a more severe form than anticipated are also considered to be unexpected.

Serious Adverse Event (SAE) or Serious Adverse Reaction: any untoward medical occurrence or effect that at any dose;

- Results in death
- Is life-threatening – refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires hospitalisation, or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect

Medical judgement should be exercised in deciding whether an AE/AR is serious in other situations. Important AE/ARs 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 of the other outcomes listed in the definition above, should also be considered serious.

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

Expected adverse events: The population of patients involved in the IPC-PLUS trial is such that a high number of adverse events are to be expected. Many of these will not be related to IMP administration or trial-related procedures, but will be as a direct consequence of the patient's underlying malignancy. Other events may occur as a result of a trial-related intervention, but are well-documented and regarded as normal reactions in the context of talc administration or IPC drainage. Expected adverse events in these settings are:

- Death due to underlying malignancy
- Admission due to underlying malignancy
- New fever after instillate
- New mild tachycardia after instillate (≤20 beats per minute over baseline)
- New pleuritic chest pain after instillate requiring simple analgesia (simple analgesia is defined as any medication which is not a morphine derivative or equivalent)
- New tachypnoea after instillate (increase in respiratory rate of ≥5 breaths per minute over baseline)
- New hypoxia after instillate (to saturation of ≤92% on air, or to a level requiring additional supplemental oxygen)
- Mild transient cough, chest pain or discomfort reasonably associated with drainage of the IPC requiring no analgesia or use of patient's standard analgesia only

7.2
Causality

The assignment of the causality of an adverse event or adverse reaction should be made by the investigator responsible for the care of the participant using the definitions in the table below (7.2.1). If any doubt about the causality exists the local investigator should inform the trial co-ordinator who will notify the Chief Investigator. The pharmaceutical companies and/or other clinicians may be asked to advise in some cases. In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the MHRA will be informed of both points of view.

7.2.1
Relationships

- Unrelated – there is no evidence of any causal relationship.
- Unlikely – there is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
- Possible – there is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
- Probable – there is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Definitely – there is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

- Not assessable - there is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

7.3
Reporting procedures

All adverse events should be recorded. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the trial coordination centre in the first instance.

7.3.1
Non serious AR/AEs

All such toxicities, whether expected or not, should be recorded in the adverse events section of the relevant case report form and on a separate adverse event form, before being sent to the trial coordination centre.

7.3.2
Expected adverse events

Expected adverse events, as listed in section 7.1, should be recorded on the appropriate CRF and on a separate adverse event form as above. However, such events need not be reported as serious adverse events (even if the criteria for such are met) unless the local principal investigator deems this to be necessary. The occurrence of “Mild transient cough, chest pain or discomfort reasonably associated with drainage of the IPC requiring no analgesia or use of patient’s standard analgesia only” is likely to be very high as this is a normal and expected part of IPC drainage, therefore this expected adverse event does not need to be reported as an AE.

7.3.3
Serious AR/AEs

Fatal or life threatening SAEs and SUSARs should be reported on the day that the local site is aware of the event. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). The responsible investigator should sign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

In the case of a SAE occurring, an SAE form should be completed and faxed to the trial coordination centre and to the sponsor within 24 hours. However, as per section 7.3.2, due to the proposed population of patients in this study, death and hospital admission due to co-morbidities are to be predictable and expected occurrences during the trial. The dates of such events should be recorded on CRFs and on adverse event forms, but need not be reported as SAEs unless the local principal investigator feels there is a clear temporal or causal relationship to a trial intervention (i.e. IPC insertion or administration of talc). In

addition, hospitalisations for elective treatment of a pre-existing condition do not need reporting as SAEs.

In the case of suspected unexpected serious adverse reactions (SUSAR), the staff at the site should either;

c) Complete the SAE case report form & send it immediately (within 24 hours, preferably by fax), signed and dated to the trial coordination centre and sponsor, together with relevant treatment forms and anonymised copies of all relevant investigations.

d) Contact the trial coordination centre by phone and then send the completed SAE form to the trial coordination centre within the following 24 hours as above.

The trial coordination centre will notify the MHRA, REC and the Sponsor of all SUSARs occurring during the trial according to the following timelines: fatal and life-threatening within 7 days of notification; and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the trial. Local investigators should also report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & Development Office.

Contact details for reporting SAEs and SUSARs are as follows:

NBT R&I office (within 24 hours).
Fax: 0117 414 9329
Email: researchsponsor@nbt.nhs.uk

Please send a copy of SAE forms to:
IPC-PLUS Trial,
Respiratory Research Unit,
Clinical Research Centre,
Southmead Hospital,
Bristol,
BS10 5NB

Tel: 0117 414 8149 (Mon to Fri 09.00 – 17.00)
Fax: 0117 414 8149 (For attention of: IPC-PLUS Trial administrators)

SECTION 8 – TRIAL INFRASTRUCTURE

8.1
Trial management group (TMG)

The TMG is responsible for the day-to-day management of the trial. The team is responsible for all aspects of the project (such as recruitment rate, budget management, protocol adherence, etc.) and for ensuring appropriate action is taken to safeguard trial participants and the quality of the study.

- Professor Nick Maskell, Chief Investigator (CI) and principal investigator for Bristol.
- Dr Rahul Bhatnagar, Trial Co-ordinator (TC) and Academic Clinical Lecturer based at Southmead Hospital in Bristol
- Dr Najib Rahman, Key investigator and principal investigator for Oxford
- Mrs Anna Morley, lead trial nurse in Bristol
- Miss Louise Allen, pleural research nurse in Bristol
- Mr Brennan Kahan, trial statistician
- Dr Emma Keenan, trial administrator

Identification of patients, insertion of IPCs and clinic-based follow-up will take place at the patient's local trial centre, by medical members of the trial team.

Routine drainage of patients' IPCs is to take place in the community. This will be performed by community nurses, lung cancer specialist nurses, or trial nurses, all of whom must be appropriately trained.

The Respiratory Research Unit at Southmead Hospital will have responsibility for authorisation, GCP and conduct, data integrity, data checking and database integrity.

Randomisation will be co-ordinated by Sealed Envelope (Sealed Envelope Ltd, Concorde House, Grenville Place, London, NW7 3SA).

The trial database is designed and maintained by the Clinical Trials and Evaluation Unit (CTEU) at the University of Bristol.

8.2
Trial steering committee (TSC)

The TSC consists of both independent members as well as researchers working on the trial. The role of the TSC is to provide overall supervision of the study and monitor the progress of the trial to ensure that it is being conducted in accordance with the protocol, relevant regulations and the principles of GCP. The Sponsor will be represented at TSC meetings but may choose to devolve this responsibility to one of the people named below. The TSC will meet at regular intervals and will comprise:

Independent chair	Professor Robert Miller
Chief Investigator	Professor Nick Maskell
Trial Co-ordinator	Dr Rahul Bhatnagar
Key Investigator	Dr Najib Rahman
Lead Trial Nurse	Mrs Anna Morley
Trial Statistician	Mr Brennan Kahan
Thoracic Cancer Specialist Nurse Advisor	Miss Sarah Smith
Independent member	Dr John Harvey
Patient representative	Mrs Karen Cooper
Independent advisory member	Professor Gary Lee

8.3
Independent data monitoring committee (IDMC)

The IDMC is independent of the trial investigators. Its role is to review study safety data and provide advice to the TSC as to whether recruitment can continue.

Independent statistician	Ms Ly-Mee Yu
Independent physician	Professor Tim Peto
Independent physician	Professor Duncan Geddes

SECTION 9 – ETHICAL ISSUES

9.1
Indwelling pleural catheters

Since the use of indwelling pleural catheters is considered to be standard practice in many centres around the world, there are no predicted ethical issues regarding their use as first-line management of malignant pleural effusions. Several studies have shown at least non-inferiority to the more established practice of traditional chest drainage and talc pleurodesis.

9.2
Talc

Talc, as used in the context proposed in this trial, is regarded as an Investigational Medicinal Product (IMP), and therefore the appropriate approval has been sought from the MHRA. No other new IMPs are to be used in the trial. There is no evidence that talc increases either morbidity or mortality in patients with malignant pleural effusions.

9.3
Consent and withdrawal

Consent for IPC insertion will occur to GMC standards, including a discussion of potential risks and alternative treatment strategies in every case. Written, informed consent for participation in the study will be obtained in every case, with adequate reflection time provided, and included information on risks and benefits of each procedure and the rationale for the study. Participants will give their permission, where appropriate, for linked anonymous blood and pleural samples to be stored and analysed at North Bristol NHS Trust (NBT), or, if from Oxford, for those samples to be transferred to NBT for storage and analysis. Participants will be followed closely as described, and treated in line with standard local practices.

Patients will have the right to withdraw consent for any part of the study at any time, without giving any reasons for doing so. (See also Section 5.1)

9.4
Data security

Fully anonymised trial documentation will be securely stored for at least 5 years after study completion and thereafter disposed of according to regulatory requirements.

SECTION 10 - FUNDING AND INSURANCE

10.1
Funding

This study is supported by an unrestricted educational grant from CareFusion (IL, USA), who are also supplying indwelling pleural catheters, drainage kits, and associated materials for the trial.

10.2
Negligent harm

North Bristol NHS trust has arrangements in place to provide for harm arising from participation in the study for which the Trust is legally liable as the UK Research Sponsor. Within the UK the NHS will have a duty of care to study participants undergoing clinical treatment, and NHS / hospital Trust indemnity operates in respect to this through the NHS Litigation Scheme. Elsewhere, any hospital or other healthcare organisation responsible for the clinical care of study participants will have an equivalent arrangement in place in respect to indemnity and/or compensation for negligent harm arising during the clinical treatment of patients to whom they owe a duty of care.

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APPENDIX 2 – Abbreviations

°C	Degrees centigrade
AE	Adverse event
AR	Adverse reaction
CI	Chief investigator
CIOMS	Council for International Organization of Medical Sciences
CRF	Case report form
CT	Computed tomography
CXR	Chest x-ray
ECOG / WHO	Eastern Co-operative Oncology Group / World Health Organisation
EDTA	Ethylenediaminetetraacetic acid
EoT	End of trial
EQ-5D	EuroQol 5D health questionnaire
GMC	General Medical Council
IDMC	Independent data monitoring committee
IMP	Investigational medicinal product
IPC	Indwelling pleural catheter
L	Litres
MDT	Multidisciplinary team
MHRA	The Medicines and Healthcare products Regulatory Agency
ml or **mls**	Millilitres
MPE	Malignant pleural effusion
NBT	North Bristol NHS Trust
NHS	National Health Service
NT-proBNP	N-Terminal pro-Brain Natriuretic Peptide
PA	Posterior - Anterior
PI	Principal investigator
PSSRU	Personal Social Services Research Unit
QoL	Quality of life
SAE	Serious adverse event
SAR	Serious adverse reaction
SmPC	Summary of the product characteristics
SOB	Shortness of breath
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SUSAR	Suspected unexpected serious adverse reaction
TC	Trial co-ordinator
TMG	Trial management group
TSC	Trial steering committee
VAS	Visual analogue scale

Appendix 3

	TIMINGS										
EVENT	Pre-screening	Consent/baseline	IPC insertion	Pre Randomisation	Randomisation	Follow-ups (Days post randomisation)					On-going (between follow-up)
						14	28	42[1]	56[1]	70	
Provide Patient Information Sheet	X										
Sign consent		X									
Thoracic ultrasound		X			X	X	X	X	X	X	
Chest x-ray		X[2]	X		X	X	X	X	X	X	
Standard blood tests		X									
Trial blood samples (Southmead and Oxford ONLY)		X									
Trial pleural fluid samples (Southmead and Oxford ONLY)			X		X	X	X	X	X	X	
Manometry			X								
Instillation of talc/placebo					X						
Community IPC drainages				X[3]							X
Drainage booklet			X								X
Daily VAS Scores				X							X
Collection of VAS booklet					X	X	X	X	X	X	
EQ-5D questionnaire		X			X	X	X	X	X	X	
QLQ-C30 questionnaire		X			X	X	X	X	X	X	
Patient diary				X							X

[1]Visits at Days 42 and 56 may be done over the telephone and therefore patient would not have chest x-ray or thoracic ultrasound

[2]Chest x-ray at baseline is only required if patient has not had a chest X-ray within the last 24 hours

[3]Minimum of 3 drainages in the community between IPC insertion and randomisation

Section 1c – Summary of protocol changes

Substantial Amendment number	Details of significant alterations to protocol	Resulting protocol version and date
1	• Clarification of randomisation target of 154 patients • All references to SF-36 QoL questionnaire removed • Added exclusion criteria: patients must have access to phone for investigator trial contact • Clarified sample collection and analysis • Clarified procedure pre-randomisation • Clarified that patients may also be excluded from randomisation for clinical reasons other than x-ray appearances • Updated summary tables and clarified pre-randomisation day nomenclature • Stipulated a time window in which patients must have first IPC drainage post-randomisation • Clarified time window in which pts may have follow-up appointments • Clarified wording in safety reporting section and highlighted expected minor side effects from talc • Updated members of trial steering committee • New sites added: Preston, Portsmouth, Bristol Royal Infirmary	**2.0** **09/07/2012**
2	• Change of principal investigator at Portsmouth site	
3	• New sites added: Worcester, North Staffordshire, North Tyneside, Middlesbrough, South Manchester and Blackpool • Creation of letter and short trial summary for district nurses • Alteration to primary endpoint, changing minimal fluid volume required for pleurodesis from 20mLs to 50mLs • Change to time limit given to patients to consider PIS • Removed requirement that trial CXR must be taken posterior-anterior (PA) specifically • Trial flow chart updated allowed patients to have follow up appointments at satellite centres • Allowance for patients to be approached as an inpatient but management must be as an outpatient for trial • Clarifications to adverse event and serious adverse event reporting procedures	**3.0** **18/12/2012**
4	• New site added: Bath	
5	• New sites added: London, Mansfield, Stockton-on-Tees and Sheffield • Clarification of wording of primary endpoint, removal of duplicate secondary endpoint and addition of new secondary endpoint	**4.0** **01/08/2013**

	• Clarification of definition of trapped lung in trial flow chart and protocol • Addition of new QoL questionnaire (QLQ-C30) for all new trial participants • Expanded the use of pleural manometry to all centres • Removed need for 0.9% saline placebo to be sources from particular manufacturer • Updated wording of how the primary outcome will be analysed • Updated membership of trial steering committee	
6	• New sites added: Northampton, Ayr, Cambridge, and Aintree • Change of inclusion criteria to require WHO performance of 2 or better to be eligible. 3 if goes to 2 after drainage. • Allow pts with previous pleurodesis as long as more than 56 days before trial entry • Relax follow-up visits by allowing day 42 and 56 to be carried out over telephone • Allow carers/relatives to perform chest drains after day 28 post randomisation visit • Extend recruitment period to May 2015 • Relaxation of manometry recordings from every 100 ml to every 100-200 ml • Updated membership of TSC	**5.0** **01/01/2014**
7	• Remove interim analysis • add cough, chest pain/discomfort following drainage to expected AEs • amend reporting procedure for mild cough, chest pain/discomfort • extend trial end date to 31/10/2016 • update R&I contact details for SAE reporting	**6.0** **09/09/2016**

Section 2a – Original analysis plan

North Bristol NHS
NHS Trust

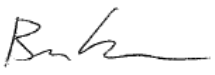
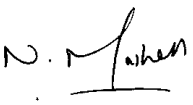
The efficacy of Indwelling Pleural Catheter placement versus IPC placement PLUS sclerosant (talc) in patients with malignant pleural effusions managed exclusively as out-patients

IPC + PLUS
TRIAL

STATISTICAL ANALYSIS PLAN

Version 1
1st July 2014

REC	**12/SC/0242**
EudraCT Number	**2012-000599-40**
ISRCTN	**73255764**

Authorised by	Signature	Date
Brennan Kahan **Trial statistician** B.Kahan@qmul.ac.uk		1st July 2014
Nick Maskell **Chief Investigator** Nick.Maskell@bristol.ac.uk		1st July 2014
Robert Miller **Trial Steering Committee Chair** Robert.Miller@ucl.ac.uk		1st July 2014

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1. BACKGROUND AND DESIGN

The main characteristics of this trial are summarised in the latest IPC-PLUS trial protocol. Please refer to this for full details.

1.1 Trial summary

Malignant pleural effusions remain a common problem with 40,000 new cases in the UK each year and up to 250,000 in the US. They are increasing in incidence as survival rates of most cancers improve and life expectancy rises.

Controlling patients' symptoms of breathlessness by removal of the pleural fluid is the cornerstone of patient management, but these effusions will usually recur without more definitive intervention.

Traditional management of malignant pleural effusions has involved an inpatient stay with placement of a chest drain. This can then be followed by instillation of a pleural sclerosing agent such as talc, which aims to minimise further fluid build-up. Despite a good success rate in studies, this approach can be expensive, time-consuming and inconvenient for patients. More recently, an alternative method has become available in the form of indwelling pleural catheters which can be inserted and managed in an outpatient setting. They have also been shown to induce a pleurodesis in a small proportion of patients, but over a longer period of time.

Theoretically, therefore, the combination of indwelling pleural catheters and talc pleurodesis through this tube should provide the optimum management for malignant pleural effusions, with improved convenience for patients and a higher pleural symphysis rate.

We aim to prove, by way of a single-blind, multicentre randomised controlled trial, that this combination of treatments is superior to the use of indwelling pleural catheters alone. This study will enrol sufficient patients to randomise 154 patients and will assess the proportion of patients with successful pleurodesis at 5 weeks post randomisation. This study aims to help to define the future gold-standard out-patient management for patients with symptomatic malignant pleural effusions.

1.2 Inclusion/Exclusion criteria

1.2.1 Inclusion criteria

1. Symptomatic malignant pleural effusion, agreed at appropriate local / regional level to require IPC, defined as pleural fluid in the context of:

    a) Histocytologically proven pleural malignancy

OR

b) Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere

OR

c) Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof

2. Expected survival greater than 2 months and WHO/ECOG PS 2 or better
3. Written informed consent to trial participation

1.2.2 Exclusion criteria

1. Age < 18 years.
2. Females who are pregnant or lactating.
3. Patient unable to provide informed consent.
4. Previous attempts at pleurodesis within the last 56 days on same side as effusion requiring management.
5. Previously documented adverse reaction to talc or lidocaine.
6. Community services unable to drain indwelling pleural catheter at least twice per week.
7. 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.
8. Other contraindication to indwelling pleural catheter insertion
9. Patient has no access to a telephone

1.2.3 Changes to inclusion/exclusion criteria

Exclusion criterion 9 was updated from that stated in the original protocol as part of amendment SA01 (09/07/2012). This amendment specified that patients must have access to a telephone to be eligible for the study.

Inclusion criterion 2 was updated from that stated in the original protocol (version 1.0, date 10/04/2014) as part of amendment SA06 (05/02/2014). This amendment clarified the WHO/ECOG performance status requirements for trial participants.

Exclusion criterion 4 was updated from that stated in the original protocol as part of amendment SA06. This amendment allowed patients who had had a previous attempt at pleurodesis to be included in the study (05/02/2014).

1.3 Trial intervention

All patients will have an IPC inserted as per normal practice. After 10 days, those remaining eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant

via the IPC (intervention group), or to receive an intrapleural placebo instillation of 0.9% sterile saline (control group).

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

2. OUTCOME MEASURES

2.1 Primary outcome measure

2.1.1 Primary outcome measure description

The primary outcome measure for this trial is the number of patients with successful pleurodesis at 5 weeks post randomisation. The choice of 5 weeks relates to the fact that patients in both treatment arms will, at the time of randomisation, have already had an IPC in situ for approximately 10 days. This means that the trial is effectively measuring pleurodesis success at 6 weeks post initial intervention (IPC insertion) – a more recognised and clinically relevant time point.

Successful 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, who should be blind to treatment allocation. Information on drainage volumes will be collected in the community and during follow-up visits as described above. The x-ray for chest opacification must have been taken after the third consecutive occasion of collection less than 50mls, and within the 10 week follow-up period. All three occasions of collection less than 50mls should also occur within the 10 week follow-up period.

Patients who drain less than 50mls of fluid on three or more occasions but who continue to have greater than 25% pleural opacification on chest x-ray due to pleural fluid (as proven by the presence of either a moderate or large effusion on contemporaneous thoracic ultrasound), will be defined as having an unsuccessful pleurodesis. If there is a clinical suspicion that the drain may be blocked then appropriate attempts to resolve this should be made prior to a definition being made.

The achievement of pleurodesis should be dated to the first drainage of less than or equal to 50mls. Even if patients achieve the requirements for pleurodesis during the trial period, they will continue to receive fortnightly follow-up as originally planned until the 70-day follow-up period is complete.

Patients who die during the 10-week trial period will be assessed for whether they achieved pleurodesis success prior to death. This requires 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, who should be blind to treatment allocation, with the x-ray having been taken after the third consecutive collection volume of less than 50mls.

2.1.2 Changes to primary outcome measure

Amendment SA03 (date 14/12/2012) revised the primary outcome measure to define successful pleurodesis as the sequential collection of 50mls rather than 20mls. This was

amended as it became clear that the drainage bottles being used in the study are unable to provide accurate measurements below 50mls of fluid.

2.2 Secondary outcome measures

2.2.1 Secondary outcome measures description

- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using the EQ-5D health questionnaire
- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days using the QLQ-C30 questionnaire
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for thoracic pain
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for breathlessness
- Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
- All-cause mortality up to 10 weeks post randomisation.
- Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
- Overall size of pleural effusion (none, small, moderate, large) at 14, 28, 42, 56, and 70 days
- Degree of septation of pleural fluid (none, light, moderate, heavy) at 14, 28, 42, 56, and 70 days.
- Pleurodesis success at 10 weeks post randomisation
- Pleurodesis success at 5 weeks, as defined by the total volume of fluid collected over a 2 week period (see below)
- Pleurodesis success at 10 weeks, as defined by the total volume of fluid collected over a 2 week period (see below)
- Further pleural procedures from randomisation to 10 weeks post-randomisation (see below
- Adverse events from randomisation to 10 weeks post-randomisation
- Serious adverse events from randomisation to 10 weeks post-randomisation

2.2.2 Clarification of secondary endpoints

Size of pleural effusion

The overall size of any effusion will be determined using a standardised data capture tool, which is to be completed by the physician performing any trial-related thoracic ultrasound scans. Effusion size is to be categorised as one of the following in all cases:

- None
- Small (fluid present only in basal area)

- Moderate (Effusion affects less than half of the hemithorax, but more than just the basal area
- Large (Effusion affects more than half of the hemithorax)

Degree of septation of pleural fluid

No septation is defined as the absence of visible septation on ultrasound. Light septation is defined as a collection with 3 or fewer septations visible on ultrasound at the maximally septated area. Moderate septation is defined as a collection with 4-9 septations visible at the maximally septated area. Heavy septation is defined as a collection with more than 9 septations visible at the maximally septated area.

Successful pleurodesis by measurement of total volume over time (Secondary endpoint)

As part of a secondary analysis, patients who have recorded drainages of less than or equal to a total of 250mls of fluid over two consecutive weeks during their follow-up period (with appropriate radiological findings) will also be defined as having a successful pleurodesis. The period of two consecutive weeks may begin with any drainage which is undertaken during the post-randomisation trial period, and ends two weeks later on the same day of the week. The drainage volume recorded on this final day is included in the total volume for the two week period. Patients must be drained no less frequently than twice per week.

In order to be defined as having a successful pleurodesis, a patient's chest x-ray must have chest opacification on the side of the IPC of less than 25%, as judged by 2 independent clinicians, who should be blind to treatment allocation. The x-ray for chest opacification must have been taken after the 2-week period's last drainage, and within the overall 10 week follow-up period.

For patients who successfully drain less than or equal to 250mls of fluid in a two week period, the date of pleurodesis is defined as the day of the first drainage in that period. All drainages which count towards the total volume must occur within the study period.

Patients who die during the follow-up period will also be assessed for pleurodesis using measurements collected prior to death. The clinical and radiological parameters used to define successful pleurodesis by volume over time remain the same as those described above.

Further pleural procedures

A further pleural procedure is defined as any of the following (provided it takes place on the side of the trial intervention):

- Therapeutic aspiration of >100mls of fluid
- Insertion of an intercostal drain for fluid drainage
- Repeat insertion of an indwelling pleural catheter
- Medical or surgical thoracoscopy

3. SAMPLE SIZE CALCULATIONS

3.1 Sample size

Talc pleurodesis alone has been shown to be up to 90% efficacious in trial conditions, and we expect the combination of talc and IPC to be at least as effective as talc alone. IPCs used alone have a more variable range for pleurodesis efficacy but it is thought to be around 50% for pulmonary or pleural malignancies, which are expected to make up the bulk of our trial cases.

In order to detect a 25% difference in pleurodesis success at 5 weeks (60% IPC alone vs 85% IPC and talc) with 90% power, a 5% significance level, and 5% loss to follow-up, we would require 154 patients (77 in each arm).

4. ANALYSIS PRINCIPLES

4.1 General analysis principles

The primary analysis for each outcome will be by intention-to-treat, meaning that all patients on whom an outcome is available will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. More information on which patients are considered to have an available outcome is available in later sections. All tests will be two-sided, and will be considered statistically significant at the 5% level.

For each analysis, the following summaries will be provided:

- The number of patients in each treatment group who are included in the analysis
- The mean (SD) or median (IQR) in each treatment group for continuous outcomes, or the number (%) of patients experiencing an event for binary or time-to-event outcomes (time-to-event outcomes will also present the median time to event in each treatment arm if applicable)
- The treatment effect (difference in means for continuous outcomes, odds ratio for binary outcomes, hazard ratio for time-to-event outcomes, rate ratio for count outcomes) with its 95% confidence interval and a p-value

All analyses will adjust for the minimisation variables (volume of pleural fluid removed in first 10 days post IPC (≤1999 mls *vs.* ≥2000 mls), malignancy subtype (ovarian and breast *vs.* mesothelioma *vs.* other), and trapped lung)[1-3]. Minimisation variables will be included as covariates in the regression model for each outcome. Volume of pleural fluid removed in the first 10 days post IPC will be included as a continuous variable, and will be assumed to have a linear relationship with the outcome.

4.2 Interim analysis

The Independent Data Monitoring Committee (IDMC) will review the trial at regular intervals to assess patient safety. Additionally, one interim analysis will be carried out after 100 patients in order to test for efficacy. The O'Brien-Fleming stopping rule will be used, which requires a p-value of <0.005 for the primary endpoint in order to stop the trial early [4]. If the trial is not stopped at the interim analysis, the O'Brien-Fleming rule requires a p-value of <0.048 at the final analysis in order to declare a statistically significant difference in the primary endpoint. The results of the interim analysis will be presented to the IDMC, who will make a recommendation to the Trial Steering Committee (TSC) as to whether the trial should stop early. This recommendation will also take into consideration other sources of evidence apart from the primary endpoint (e.g. secondary outcomes and safety data).

4.3 Analysis of primary outcome

The primary outcome (successful pleurodesis at 5 weeks post randomisation) will be analysed using a competing risk time-to-event regression model, with mortality as the competing risk. Patients who do not experience either the primary outcome or mortality will be censored at 5 weeks post randomisation, or at the point of last contact if they are lost to follow-up before 5 weeks post randomisation.

4.4 Analysis of secondary outcomes

4.4.1 Successful pleurodesis at 10 weeks

Successful pleurodesis at 10 weeks will be analysed in the same manner as successful pleurodesis at 5 weeks.

4.4.2 Successful pleurodesis at 5 and 10 weeks (based on total volume drained over 2 weeks)

These outcomes will be analysed in the same manner as successful pleurodesis at 5 and 10 weeks based on sequential measurements.

4.4.3 Mortality

All-cause mortality up to 10 weeks post randomisation will be analysed using a logistic regression model.

4.4.4 Thoracic pain

Self-reported VAS scores for thoracic pain will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. The analysis will adjust for the baseline value of thoracic pain (in addition to the minimisation factors, as mentioned in section 5.1). Missing baseline values of thoracic pain will be imputed using mean imputation [5]. The analysis will be performed in Stata as follows:

xtmixed *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

where *outcome* refers to thoracic pain, *treat* refers to the treatment variable, *time* refers to the study day, and *covariates* refers to the covariates to be included in the analysis. Treatment effects will be presented at 14, 28, 42, 56, and 70 days.

4.4.5 Breathlessness

Self-reported VAS scores for breathlessness will be analysed using the same methods as for thoracic pain.

4.4.6 Volume of pleural fluid drained

The total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation will be analysed using a linear regression model.

4.4.7 Hospital inpatient bed-days

The number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation will be analysed using a negative binomial regression model. The number of days of follow-up will be included in the model as an offset (i.e. the model will include a term for the log-transformed number of days of follow-up for each patient, with the parameter constrained to one).

4.4.8 Overall size of pleural effusion

The overall size of the pleural effusion will be analysed using a mixed-effects ordered logistic regression model, with a treatment-by-time interaction. The baseline value of the outcome will be included in the model as a covariate. The analysis will be performed in Stata as follows:

meologit *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

4.4.8 Degree of loculation of pleural fluid

The degree of loculation of pleural will be analysed using the same methods as the overall size of the pleural effusion.

4.4.9 EQ-5D

Self-reported quality of life status using the EQ-5D questionnaire will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. The analysis will be performed in Stata as follows:

xtmixed *outcome treat##time covariates || subject id:, noconstant residual(unstructured, t(time))*

where *outcome* refers to the EQ-5D score, *treat* refers to the treatment variable, *time* refers to the study visit, and *covariates* refers to the covariates to be included in the analysis. In addition to the minimisation factors, this analysis will also adjust for baseline EQ-5D. Missing values of baseline EQ-5D will be imputed using mean imputation [5].

If this analysis model does not converge (possibly due to the presence of too many variance parameters), we will instead use the following analysis model:

xtmixed *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

4.4.10 QLQ-C30

Self-reported quality of life status using the QLQ-C30 questionnaire will be analysed using the same methods as the EQ-5D.

4.4.11 Further pleural procedures

Further pleural procedures will be analysed using a competing risk time-to-event regression model, with mortality as the competing risk. Patients who do not experience either an event or mortality will be censored at 10 weeks post randomisation, or at the point of last contact if they are lost to follow-up before 10 weeks post randomisation.

4.4.12 Adverse events

Adverse events will be analysed using a logistic regression model.

4.4.13 Serious adverse events

Serious adverse events will be analysed using a logistic regression model.

4.5 Subgroup analyses

Subgroup analyses will be performed for the primary outcome using an interaction test (i.e. an interaction term between the treatment and the baseline covariate will be added to the regression model), and will be considered statistically significant at the 5% level. Results from subgroup analyses will be viewed as hypothesis generating, and will not be used to make definitive statements about treatment efficacy in a specific subgroup of patients. The following subgroup analyses will be performed:

Patients receiving chemotherapy at baseline vs those not receiving chemotherapy at baseline
Previous radiotherapy to chest vs no previous radiotherapy to chest
WHO performance status 0-1 vs 2-3
Patients on NSAIDS at baseline vs those not on NSAIDS at baseline.
Presence of trapped lung at baseline vs. no trapped lung
Volume of pleural fluid removed in first 10 days post IPC (≤1999 mls vs. ≥2000 mls)

In addition to the above, a further analysis will be performed comparing rates of adverse events between those patients who are drained by family members after day 28 and those who continue to be drained by healthcare professionals. The analysis will only take place if, at the end of the study, there are 30 patients who have undergone family drainage.

4.6 Missing data

The primary outcome will be considered missing if the patient has fewer than 3 pleural drainage measurements. If the patient has 3 or more consecutive pleural drainage

measurements of less than 50mls of fluid, but does not have an x-ray for chest opacification taken after the 3rd measurement, they will be considered missing. If the patient has 3 or more pleural drainage measurements, but not 3 consecutive measurements of less than 50mls of fluid, they will be considered as unsuccessful, regardless of whether they have an x-ray for chest opacification taken. Pleurodesis success at 10 weeks, and pleurodesis success at 5 and 10 weeks based on total volume drained over 2 weeks will be assessed similarly.

EQ-5D, QLQ-C30, thoracic pain, breathlessness, overall size of the pleural effusion, and degree of septation of pleural fluid will be considered missing if no post-randomisation measurements are recorded.

Further pleural procedures, number of days in hospital, adverse events, and serious adverse events will be considered missing if the patient attends no follow-up visits, and outcome records are not available.

All-cause mortality will be considered missing if we are unable to obtain information on whether the patient was alive at the end of follow-up.

4.7 Sensitivity analyses

4.7.1 Missing data

Sensitivity to missing data for the primary outcome will be assessed under a range of missing-not-at-random scenarios. This will be performed using the following formula:

$$\Delta = \Delta_{CC} + Y_1P_1 - Y_2P_2$$

where Δ is the treatment effect under the missing-not-at-random scenario, Δ_{CC} is the treatment effect under a complete case scenario (i.e. where patients with a missing outcome are excluded), P_1 and P_2 are the proportion of patients who were excluded in groups 1 and 2 respectively, and Y_1 and Y_2 are the proportion of patients in treatment group 1 and 2 with missing data who are assumed to experience an event (i.e. who experience the primary outcome). We assume that the standard error for Δ is approximately equal to the standard error for $\Delta_{CC.}$

Y_2 will be varied between 10%, 25%, 50%, 75%, and 90% and for each value of Y_2, Y_1 will be varied between Y_2-10%, Y_2, and Y_2+10%. For example, for Y_2=25%, Y_1 will vary between 15%, 25%, and 35%.

For each scenario, a treatment effect and 95% confidence interval will be calculated, which will be compared with results from the main analysis of the primary outcome to see if conclusions are affected by different assumptions regarding the missing data.

4.7.2 Outcome definition

The primary outcome is defined as missing if patients have 3 or more consecutive pleural drainage measurements of less than 50mls of fluid, but no x-ray for chest opacification taken after the 3rd measurement. We will assess the sensitivity of this definition by re-analysing the primary outcome by including these patients as having had successful pleurodesis.

4.8 Other analyses

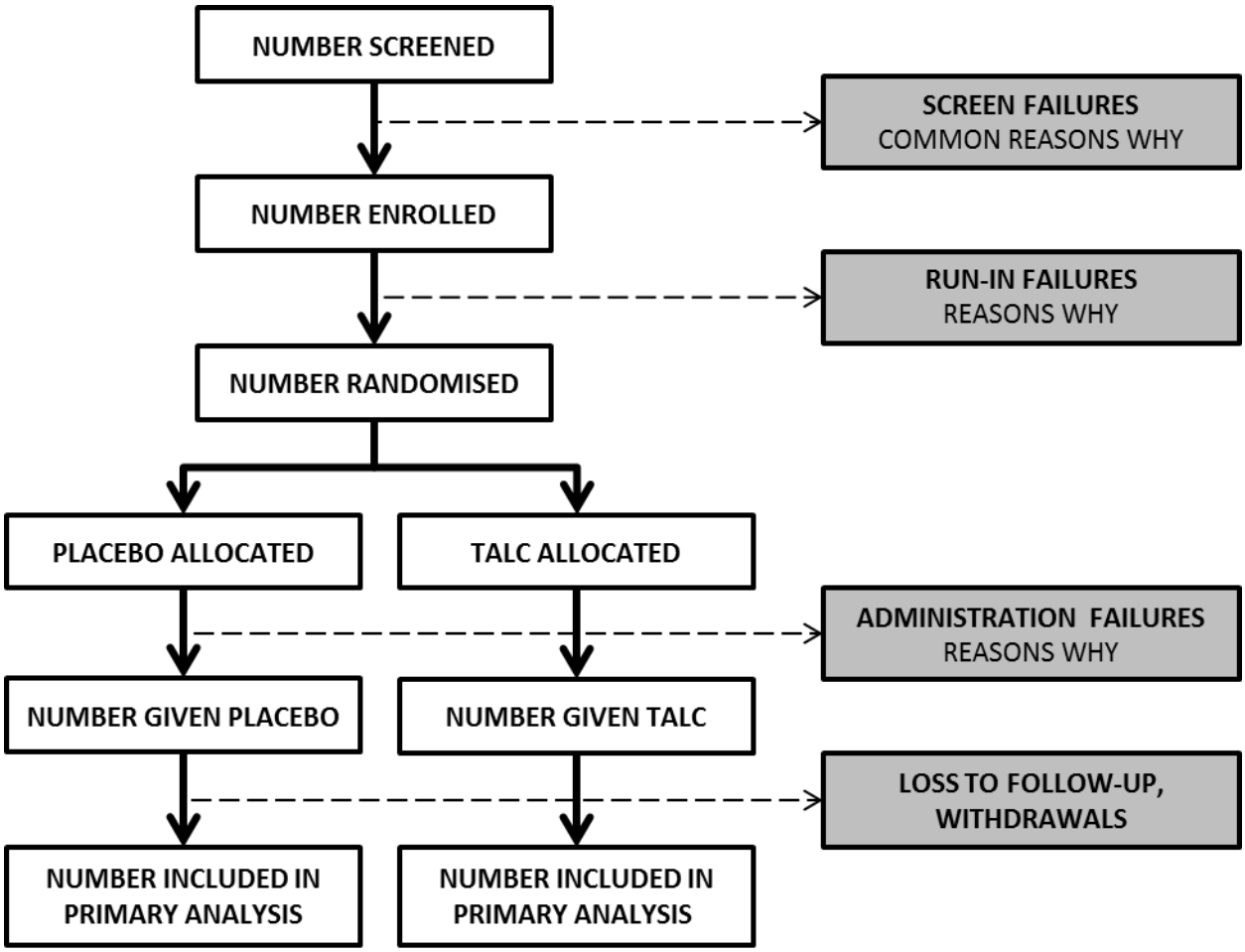
In addition to the above, data being collected as part of the IPC-PLUS trial may also be used to undertake further sub-studies, the details of which are beyond the scope of this analysis plan. These may include, but are not limited to:

- The relationship between baseline pleural manometric readings and rates of trapped lung and pleurodesis success
- A full health economic analysis
- The relationship between blood and/or fluid NT-ProBNP and pleurodesis success

5. DATA SUMMARIES

5.1 CONSORT flow chart

The following information will be provided in the form of a flow chart:



5.2 Summary graphs

The following outcomes will be displayed in the form of Kaplan-Meier survival curves:

- Pleurodesis success (as defined by consecutive volume measurement) up to 10 weeks
- Pleurodesis success (as defined by total fluid volume measurement) up to 10 weeks
- All-cause mortality

The following outcomes will be displayed in the form of two adjacent graphs; the first detailing the raw scores for the outcome (beginning with the baseline value), the second demonstrating the treatment effect. Each graph will indicate 95% confidence intervals and will provide measurements at the 14, 28, 42, 56, and 70 day time points:

- Quality of life measures (EQ-5D and QLQ-C30)
- Overall size of pleural effusion
- Degree of pleural fluid septation
- VAS scores (for breathlessness and thoracic pain)

5.3 Tables

5.3.1 Table 1 – Baseline characteristics

	Talc slurry (n=…)	Placebo (n=…)	Number missing (talc, placebo)
Age – mean (SD)			
Male – no. (%)			
Smoking status – no. (%)			
Current smoker			
Ex-smoker			
Never-smoker			
WHO performance status at randomisation – no. (%)			
0			
1			
2			
3			
4			
Underlying cancer type – no. (%)			
Lung			
Mesothelioma			
Breast or ovary			
Lymphoma			
Gastrointestinal			
Genitourinary			
Other			
Unknown			
Receiving chemotherapy – no. (%)			
Previous pleural intervention on same side of effusion in			

previous 3 months – no. (%)			
Length of time with symptoms – no. (%)			
< 1 month			
1-2 months			
> 2 months			
Chest pain (VAS) at randomisation – mean (SD)			
Breathlessness (VAS) at randomisation – mean (SD)			
Evidence of lung entrapment – no. (%)			
Total volume of fluid drained up to randomisation – mean (SD)			

5.3.2 Table 2 – Results for pleurodesis success

	Number included in analysis		**Summary measure**			
Outcome	Talc slurry (n=…)	Placebo (n=…)	Talc slurry	Placebo	Treatment effect (talc vs placebo) and 95% CI	P-value
Pleurodesis success at 5 weeks* (primary outcome) – no. (%)						
Pleurodesis success at 10 weeks* – no. (%)						
Pleurodesis success at 5 weeks* (defined by total fluid drained over two weeks) – no. (%)						

Pleurodesis success at 10 weeks* (defined by total fluid drained over two weeks) – no. (%)						
Further pleural procedures up to 10 weeks* - no. (%)						

*Treatment effects are hazard ratios

5.3.3 Table 3 – Results for secondary outcomes

	Number included in analysis		Summary measure			
Outcome	Talc slurry (n=…)	Placebo (n=…)	Talc slurry	Placebo	Treatment effect (talc vs placebo) and 95% CI	P-value
All-cause mortality up to 10 weeks* – no. (%)						
Disease-related mortality up to 10 weeks – no.(%)						
Non disease-related mortality up to 10 weeks – no. (%)						
Total volume of pleural fluid drained up to 10 weeks – mean (SD)						
Hospital inpatient bed days** – mean (SD)						
Thoracic pain*** – mean (SD)						
14						
28						
42						
56						
70						
Breathlessness*** – mean (SD)						
14						
28						
42						
56						
70						
EQ-5D*** – mean (SD)						
14						

28						
42						
56						
70						
QLQ-C30*** – mean (SD)						
14						
28						
42						
56						
70						
Overall size of pleural effusion						
Degree of septation of pleural fluid						
Adverse events* – no. (%)						
Serious adverse events* – no. (%)						

*Treatment effects are odds ratios

**Treatment effects are rate ratios

***Treatment effects are difference in means

6. REFERENCES

1. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2012;31(4):328-40. Epub 2011/12/06.
2. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ. 2012;345:e5840. Epub 2012/09/18.
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Section 2b – Final analysis plan

North Bristol NHS
NHS Trust

The efficacy of Indwelling Pleural Catheter placement versus IPC placement PLUS sclerosant (talc) in patients with malignant pleural effusions managed exclusively as out-patients

IPC + PLUS
TRIAL

STATISTICAL ANALYSIS PLAN

Version 2
2nd December 2016

REC	**12/SC/0242**
EudraCT Number	**2012-000599-40**
ISRCTN	**73255764**

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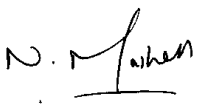
Nick Maskell **Chief Investigator** Nick.Maskell@bristol.ac.uk		2nd December 2016
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1. BACKGROUND AND DESIGN

The main characteristics of this trial are summarised in the latest IPC-PLUS trial protocol. Please refer to this for full details.

1.1 Trial summary

Malignant pleural effusions remain a common problem with 40,000 new cases in the UK each year and up to 250,000 in the US. They are increasing in incidence as survival rates of most cancers improve and life expectancy rises.

Controlling patients' symptoms of breathlessness by removal of the pleural fluid is the cornerstone of patient management, but these effusions will usually recur without more definitive intervention.

Traditional management of malignant pleural effusions has involved an inpatient stay with placement of a chest drain. This can then be followed by instillation of a pleural sclerosing agent such as talc, which aims to minimise further fluid build-up. Despite a good success rate in studies, this approach can be expensive, time-consuming and inconvenient for patients. More recently, an alternative method has become available in the form of indwelling pleural catheters which can be inserted and managed in an outpatient setting. They have also been shown to induce a pleurodesis in a small proportion of patients, but over a longer period of time.

Theoretically, therefore, the combination of indwelling pleural catheters and talc pleurodesis through this tube should provide the optimum management for malignant pleural effusions, with improved convenience for patients and a higher pleural symphysis rate.

We aim to prove, by way of a single-blind, multicentre randomised controlled trial, that this combination of treatments is superior to the use of indwelling pleural catheters alone. This study will enrol sufficient patients to randomise 154 patients and will assess the proportion of patients with successful pleurodesis at 5 weeks post randomisation. This study aims to help to define the future gold-standard out-patient management for patients with symptomatic malignant pleural effusions.

1.2 Inclusion/Exclusion criteria

1.2.1 Inclusion criteria

4. Symptomatic malignant pleural effusion, agreed at appropriate local / regional level to require IPC, defined as pleural fluid in the context of:

    d) Histocytologically proven pleural malignancy

OR

e) Otherwise unexplained pleural effusion in the context of clinically proven cancer elsewhere

OR

f) Radiologically proven pleural malignancy as diagnosed in normal clinical practice on thoracic CT in the absence of histocytological proof

5. Expected survival greater than 2 months and WHO/ECOG PS 2 or better
6. Written informed consent to trial participation

1.2.2 Exclusion criteria

10. Age < 18 years.
11. Females who are pregnant or lactating.
12. Patient unable to provide informed consent.
13. Previous attempts at pleurodesis within the last 56 days on same side as effusion requiring management.
14. Previously documented adverse reaction to talc or lidocaine.
15. Community services unable to drain indwelling pleural catheter at least twice per week.
16. 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.
17. Other contraindication to indwelling pleural catheter insertion
18. Patient has no access to a telephone

1.2.3 Changes to inclusion/exclusion criteria

Exclusion criterion 9 was updated from that stated in the original protocol as part of amendment SA01 (09/07/2012). This amendment specified that patients must have access to a telephone to be eligible for the study.

Inclusion criterion 2 was updated from that stated in the original protocol (version 1.0, date 10/04/2014) as part of amendment SA06 (05/02/2014). This amendment clarified the WHO/ECOG performance status requirements for trial participants.

Exclusion criterion 4 was updated from that stated in the original protocol as part of amendment SA06. This amendment allowed patients who had had a previous attempt at pleurodesis to be included in the study (05/02/2014).

1.3 Trial intervention

All patients will have an IPC inserted as per normal practice. After 10 days, those remaining eligible for trial entry will be assigned randomly (1:1) to either receive talc slurry sclerosant

via the IPC (intervention group), or to receive an intrapleural placebo instillation of 0.9% sterile saline (control group).

Patients will remain blind to treatment allocation, but clinicians and members of the trial team will not be blinded. Other healthcare professionals who are involved in participants' care will not be made aware of treatment allocation routinely, but may be made aware of treatment allocation in the course of routine clinical care, if necessary.

1.4 Changes from previous versions

Version 1.0 of this document stipulated that an interim analysis for efficacy be performed after 100 patients had been recruited, using the O'Brien-Fleming stopping rule for the primary endpoint. This stopping rule required a significance threshold for the primary outcomeof 0.048 at final analysis. However, because patient recruitment was quicker than anticipated, the TSC felt that by the time data would be ready for the interim analysis (i.e. after the follow-up was complete for the 100th patient, and the primary outcome had been adjudicated by two independent clinicians), the overall sample size target of 154 patients would be almost completed, rendering an interim analysis unnecessary. Therefore, the IDMC and TSC recommended that the interim analysis not be undertaken, and that the significance threshold for the final analysis be set at 0.05. This change was implemented to the trial protocol in version 6.0 (9/9/16), as part of substantial amendment SA7 (approved 7/10/16).

2. OUTCOME MEASURES

2.1 Primary outcome measure

2.1.1 Primary outcome measure description

The primary outcome measure for this trial is the number of patients with successful pleurodesis at 5 weeks post randomisation. The choice of 5 weeks relates to the fact that patients in both treatment arms will, at the time of randomisation, have already had an IPC in situ for approximately 10 days. This means that the trial is effectively measuring pleurodesis success at 6 weeks post initial intervention (IPC insertion) – a more recognised and clinically relevant time point.

Successful 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, who should be blind to treatment allocation. Information on drainage volumes will be collected in the community and during follow-up visits as described above. The x-ray for chest opacification must have been taken after the third consecutive occasion of collection less than 50mls, and within the 10 week follow-up period. All three occasions of collection less than 50mls should also occur within the 10 week follow-up period.

Patients who drain less than 50mls of fluid on three or more occasions but who continue to have greater than 25% pleural opacification on chest x-ray due to pleural fluid (as proven by the presence of either a moderate or large effusion on contemporaneous thoracic ultrasound), will be defined as having an unsuccessful pleurodesis. If there is a clinical suspicion that the drain may be blocked then appropriate attempts to resolve this should be made prior to a definition being made.

The achievement of pleurodesis should be dated to the first drainage of less than or equal to 50mls. Even if patients achieve the requirements for pleurodesis during the trial period, they will continue to receive fortnightly follow-up as originally planned until the 70-day follow-up period is complete.

Patients who die during the 10-week trial period will be assessed for whether they achieved pleurodesis success prior to death. This requires 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, who should be blind to treatment allocation, with the x-ray having been taken after the third consecutive collection volume of less than 50mls.

2.1.2 Changes to primary outcome measure

Amendment SA03 (date 14/12/2012) revised the primary outcome measure to define successful pleurodesis as the sequential collection of 50mls rather than 20mls. This was

amended as it became clear that the drainage bottles being used in the study are unable to provide accurate measurements below 50mls of fluid.

2.2 Secondary outcome measures

2.2.1 Secondary outcome measures description

- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days, using the EQ-5D health questionnaire
- Self-reported quality of life status, measured at 14, 28, 42, 56, and 70 days using the QLQ-C30 questionnaire
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for thoracic pain
- Self-reported VAS scores, measured daily from randomisation to 10 weeks post-randomisation, for breathlessness
- Total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation
- All-cause mortality up to 10 weeks post randomisation.
- Number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation
- Overall size of pleural effusion (none, small, moderate, large) at 14, 28, 42, 56, and 70 days
- Degree of septation of pleural fluid (none, light, moderate, heavy) at 14, 28, 42, 56, and 70 days.
- Pleurodesis success at 10 weeks post randomisation
- Pleurodesis success at 5 weeks, as defined by the total volume of fluid collected over a 2 week period (see below)
- Pleurodesis success at 10 weeks, as defined by the total volume of fluid collected over a 2 week period (see below)
- Further pleural procedures from randomisation to 10 weeks post-randomisation (see below
- Adverse events from randomisation to 10 weeks post-randomisation
- Serious adverse events from randomisation to 10 weeks post-randomisation

2.2.2 Clarification of secondary endpoints

Size of pleural effusion

The overall size of any effusion will be determined using a standardised data capture tool, which is to be completed by the physician performing any trial-related thoracic ultrasound scans. Effusion size is to be categorised as one of the following in all cases:

- None
- Small (fluid present only in basal area)

- Moderate (Effusion affects less than half of the hemithorax, but more than just the basal area
- Large (Effusion affects more than half of the hemithorax)

Degree of septation of pleural fluid

No septation is defined as the absence of visible septation on ultrasound. Light septation is defined as a collection with 3 or fewer septations visible on ultrasound at the maximally septated area. Moderate septation is defined as a collection with 4-9 septations visible at the maximally septated area. Heavy septation is defined as a collection with more than 9 septations visible at the maximally septated area.

Successful pleurodesis by measurement of total volume over time (Secondary endpoint)

As part of a secondary analysis, patients who have recorded drainages of less than or equal to a total of 250mls of fluid over two consecutive weeks during their follow-up period (with appropriate radiological findings) will also be defined as having a successful pleurodesis. The period of two consecutive weeks may begin with any drainage which is undertaken during the post-randomisation trial period, and ends two weeks later on the same day of the week. The drainage volume recorded on this final day is included in the total volume for the two week period. Patients must be drained no less frequently than twice per week.

In order to be defined as having a successful pleurodesis, a patient's chest x-ray must have chest opacification on the side of the IPC of less than 25%, as judged by 2 independent clinicians, who should be blind to treatment allocation. The x-ray for chest opacification must have been taken after the 2-week period's last drainage, and within the overall 10 week follow-up period.

For patients who successfully drain less than or equal to 250mls of fluid in a two week period, the date of pleurodesis is defined as the day of the first drainage in that period. All drainages which count towards the total volume must occur within the study period.

Patients who die during the follow-up period will also be assessed for pleurodesis using measurements collected prior to death. The clinical and radiological parameters used to define successful pleurodesis by volume over time remain the same as those described above.

Further pleural procedures

A further pleural procedure is defined as any of the following (provided it takes place on the side of the trial intervention):

- Therapeutic aspiration of >100mls of fluid
- Insertion of an intercostal drain for fluid drainage
- Repeat insertion of an indwelling pleural catheter
- Medical or surgical thoracoscopy

3. SAMPLE SIZE CALCULATIONS

3.1 Sample size

Talc pleurodesis alone has been shown to be up to 90% efficacious in trial conditions, and we expect the combination of talc and IPC to be at least as effective as talc alone. IPCs used alone have a more variable range for pleurodesis efficacy but it is thought to be around 50% for pulmonary or pleural malignancies, which are expected to make up the bulk of our trial cases.

In order to detect a 25% difference in pleurodesis success at 5 weeks (60% IPC alone vs 85% IPC and talc) with 90% power, a 5% significance level, and 5% loss to follow-up, we would require 154 patients (77 in each arm).

4. ANALYSIS PRINCIPLES

4.1 General analysis principles

The primary analysis for each outcome will be by intention-to-treat, meaning that all patients on whom an outcome is available will be included in the analysis, and will be analysed according to the treatment group to which they were randomised. More information on which patients are considered to have an available outcome is available in later sections. All tests will be two-sided, and will be considered statistically significant at the 5% level.

For each analysis, the following summaries will be provided:

- The number of patients in each treatment group who are included in the analysis
- The mean (SD) or median (IQR) in each treatment group for continuous outcomes, or the number (%) of patients experiencing an event for binary or time-to-event outcomes (time-to-event outcomes will also present the median time to event in each treatment arm if applicable)
- The treatment effect (difference in means for continuous outcomes, odds ratio for binary outcomes, hazard ratio for time-to-event outcomes, rate ratio for count outcomes) with its 95% confidence interval and a p-value

All analyses will adjust for the minimisation variables (volume of pleural fluid removed in first 10 days post IPC (≤1999 mls *vs.* ≥2000 mls), malignancy subtype (ovarian and breast *vs.* mesothelioma *vs.* other), and trapped lung)[1-3]. Minimisation variables will be included as covariates in the regression model for each outcome. Volume of pleural fluid removed in the first 10 days post IPC will be included as a continuous variable, and will be assumed to have a linear relationship with the outcome.

4.2 Interim analysis

The Independent Data Monitoring Committee (IDMC) will review the trial at regular intervals to assess patient safety. There will be no formal interim analyses for efficacy (see section 1.4).

4.3 Analysis of primary outcome

The primary outcome (successful pleurodesis at 5 weeks post randomisation) will be analysed using a competing risk time-to-event regression model, with mortality as the competing risk. Patients who do not experience either the primary outcome or mortality will be censored at 5 weeks post randomisation, or at the point of last contact if they are lost to follow-up before 5 weeks post randomisation.

4.4 Analysis of secondary outcomes

4.4.1 Successful pleurodesis at 10 weeks

Successful pleurodesis at 10 weeks will be analysed in the same manner as successful pleurodesis at 5 weeks.

4.4.2 Successful pleurodesis at 5 and 10 weeks (based on total volume drained over 2 weeks)

These outcomes will be analysed in the same manner as successful pleurodesis at 5 and 10 weeks based on sequential measurements.

4.4.3 Mortality

All-cause mortality up to 10 weeks post randomisation will be analysed using a logistic regression model.

4.4.4 Thoracic pain

Self-reported VAS scores for thoracic pain will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. The analysis will adjust for the baseline value of thoracic pain (in addition to the minimisation factors, as mentioned in section 5.1). Missing baseline values of thoracic pain will be imputed using mean imputation [4]. The analysis will be performed in Stata as follows:

xtmixed *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

where *outcome* refers to thoracic pain, *treat* refers to the treatment variable, *time* refers to the study day, and *covariates* refers to the covariates to be included in the analysis. Treatment effects will be presented at 14, 28, 42, 56, and 70 days.

4.4.5 Breathlessness

Self-reported VAS scores for breathlessness will be analysed using the same methods as for thoracic pain.

4.4.6 Volume of pleural fluid drained

The total volume of pleural fluid drained from randomisation to 10 weeks post-randomisation will be analysed using a linear regression model.

4.4.7 Hospital inpatient bed-days

The number of hospital inpatient bed-days required from randomisation to 10 weeks post-randomisation will be analysed using a negative binomial regression model. The number of

days of follow-up will be included in the model as an offset (i.e. the model will include a term for the log-transformed number of days of follow-up for each patient, with the parameter constrained to one).

4.4.8 Overall size of pleural effusion

The overall size of the pleural effusion will be analysed using a mixed-effects ordered logistic regression model, with a treatment-by-time interaction. The baseline value of the outcome will be included in the model as a covariate. The analysis will be performed in Stata as follows:

meologit *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

4.4.8 Degree of loculation of pleural fluid

The degree of loculation of pleural will be analysed using the same methods as the overall size of the pleural effusion.

4.4.9 EQ-5D

Self-reported quality of life status using the EQ-5D questionnaire will be analysed using a mixed-effects linear regression model, with a treatment-by-time interaction. The analysis will be performed in Stata as follows:

xtmixed *outcome treat##time covariates || subject id:, noconstant residual(unstructured, t(time))*

where *outcome* refers to the EQ-5D score, *treat* refers to the treatment variable, *time* refers to the study visit, and *covariates* refers to the covariates to be included in the analysis. In addition to the minimisation factors, this analysis will also adjust for baseline EQ-5D. Missing values of baseline EQ-5D will be imputed using mean imputation [4].

If this analysis model does not converge (possibly due to the presence of too many variance parameters), we will instead use the following analysis model:

xtmixed *outcome treat##c.time covariates || subject id: time, covariance(unstructured)*

4.4.10 QLQ-C30

Self-reported quality of life status using the QLQ-C30 questionnaire will be analysed using the same methods as the EQ-5D.

4.4.11 Further pleural procedures

Further pleural procedures will be analysed using a competing risk time-to-event regression model, with mortality as the competing risk. Patients who do not experience either an event

or mortality will be censored at 10 weeks post randomisation, or at the point of last contact if they are lost to follow-up before 10 weeks post randomisation.

4.4.12 Adverse events

Adverse events will be analysed using a logistic regression model.

4.4.13 Serious adverse events

Serious adverse events will be analysed using a logistic regression model.

4.5 Subgroup analyses

Subgroup analyses will be performed for the primary outcome using an interaction test (i.e. an interaction term between the treatment and the baseline covariate will be added to the regression model), and will be considered statistically significant at the 5% level. Results from subgroup analyses will be viewed as hypothesis generating, and will not be used to make definitive statements about treatment efficacy in a specific subgroup of patients. The following subgroup analyses will be performed:

Patients receiving chemotherapy at baseline vs those not receiving chemotherapy at baseline
Previous radiotherapy to chest vs no previous radiotherapy to chest
WHO performance status 0-1 vs 2-3
Patients on NSAIDS at baseline vs those not on NSAIDS at baseline.
Presence of trapped lung at baseline vs. no trapped lung
Volume of pleural fluid removed in first 10 days post IPC (≤1999 mls vs. ≥2000 mls)

In addition to the above, a further analysis will be performed comparing rates of adverse events between those patients who are drained by family members after day 28 and those who continue to be drained by healthcare professionals. The analysis will only take place if, at the end of the study, there are 30 patients who have undergone family drainage.

4.6 Missing data

The primary outcome will be considered missing if the patient has fewer than 3 pleural drainage measurements. If the patient has 3 or more consecutive pleural drainage measurements of less than 50mls of fluid, but does not have an x-ray for chest opacification taken after the 3rd measurement, they will be considered missing. If the patient has 3 or more pleural drainage measurements, but not 3 consecutive measurements of less than 50mls of fluid, they will be considered as unsuccessful, regardless of whether they have an x-ray for chest opacification taken. Pleurodesis success at 10 weeks, and pleurodesis success at 5 and 10 weeks based on total volume drained over 2 weeks will be assessed similarly.

EQ-5D, QLQ-C30, thoracic pain, breathlessness, overall size of the pleural effusion, and degree of septation of pleural fluid will be considered missing if no post-randomisation measurements are recorded.

Further pleural procedures, number of days in hospital, adverse events, and serious adverse events will be considered missing if the patient attends no follow-up visits, and outcome records are not available.

All-cause mortality will be considered missing if we are unable to obtain information on whether the patient was alive at the end of follow-up.

4.7 Sensitivity analyses

4.7.1 Missing data

Sensitivity to missing data for the primary outcome will be assessed under a range of missing-not-at-random scenarios. This will be performed using the following formula:

$$\Delta = \Delta_{CC} + Y_1P_1 - Y_2P_2$$

where Δ is the treatment effect under the missing-not-at-random scenario, Δ_{CC} is the treatment effect under a complete case scenario (i.e. where patients with a missing outcome are excluded), P_1 and P_2 are the proportion of patients who were excluded in groups 1 and 2 respectively, and Y_1 and Y_2 are the proportion of patients in treatment group 1 and 2 with missing data who are assumed to experience an event (i.e. who experience the primary outcome). We assume that the standard error for Δ is approximately equal to the standard error for $\Delta_{CC.}$

Y_2 will be varied between 10%, 25%, 50%, 75%, and 90% and for each value of Y_2, Y_1 will be varied between Y_2-10%, Y_2, and Y_2+10%. For example, for Y_2=25%, Y_1 will vary between 15%, 25%, and 35%.

For each scenario, a treatment effect and 95% confidence interval will be calculated, which will be compared with results from the main analysis of the primary outcome to see if conclusions are affected by different assumptions regarding the missing data.

4.7.2 Outcome definition

The primary outcome is defined as missing if patients have 3 or more consecutive pleural drainage measurements of less than 50mls of fluid, but no x-ray for chest opacification taken after the 3rd measurement. We will assess the sensitivity of this definition by re-analysing the primary outcome by including these patients as having had successful pleurodesis.

4.8 Other analyses

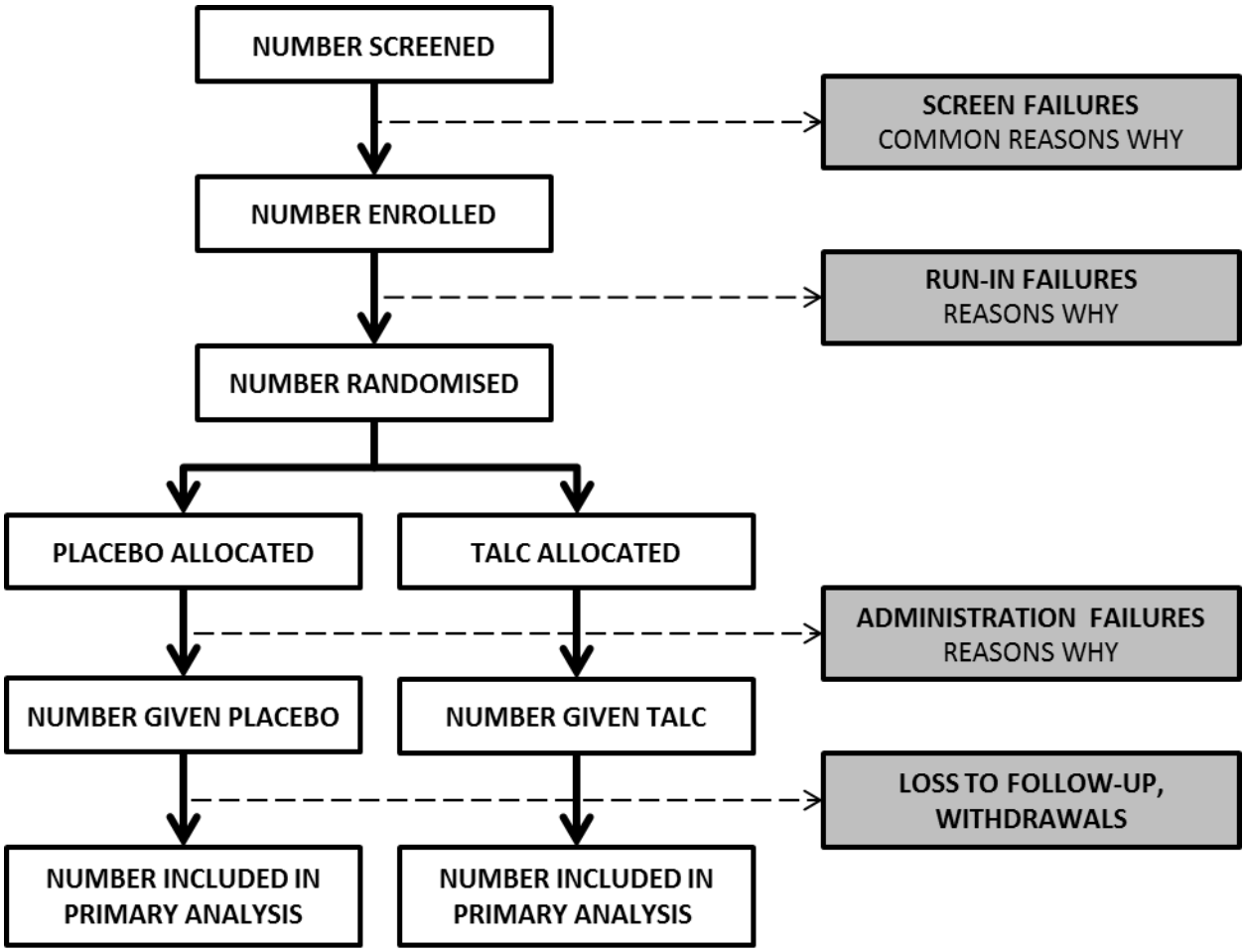
In addition to the above, data being collected as part of the IPC-PLUS trial may also be used to undertake further sub-studies, the details of which are beyond the scope of this analysis plan. These may include, but are not limited to:

- The relationship between baseline pleural manometric readings and rates of trapped lung and pleurodesis success
- A full health economic analysis
- The relationship between blood and/or fluid NT-ProBNP and pleurodesis success

5. DATA SUMMARIES

5.1 CONSORT flow chart

The following information will be provided in the form of a flow chart:



5.2 Summary graphs

The following outcomes will be displayed in the form of Kaplan-Meier survival curves:

- Pleurodesis success (as defined by consecutive volume measurement) up to 10 weeks
- Pleurodesis success (as defined by total fluid volume measurement) up to 10 weeks
- All-cause mortality

The following outcomes will be displayed in the form of two adjacent graphs; the first detailing the raw scores for the outcome (beginning with the baseline value), the second demonstrating the treatment effect. Each graph will indicate 95% confidence intervals and will provide measurements at the 14, 28, 42, 56, and 70 day time points:

- Quality of life measures (EQ-5D and QLQ-C30)
- Overall size of pleural effusion
- Degree of pleural fluid septation
- VAS scores (for breathlessness and thoracic pain)

5.3 Tables

5.3.1 Table 1 – Baseline characteristics

	Talc slurry (n=…)	Placebo (n=…)	Number missing (talc, placebo)
Age – mean (SD)			
Male – no. (%)			
Smoking status – no. (%)			
Current smoker			
Ex-smoker			
Never-smoker			
WHO performance status at randomisation – no. (%)			
0			
1			
2			
3			
4			
Underlying cancer type – no. (%)			
Lung			
Mesothelioma			
Breast or ovary			
Lymphoma			
Gastrointestinal			
Genitourinary			
Other			
Unknown			
Receiving chemotherapy – no. (%)			
Previous pleural intervention on same side of effusion in			

previous 3 months – no. (%)			
Length of time with symptoms – no. (%)			
< 1 month			
1-3 months			
> 2 months			
Chest pain (VAS) at randomisation – mean (SD)			
Breathlessness (VAS) at randomisation – mean (SD)			
Evidence of lung entrapment – no. (%)			
Total volume of fluid drained up to randomisation – mean (SD)			

5.3.2 Table 2 – Results for pleurodesis success

	Number included in analysis		**Summary measure**			
Outcome	Talc slurry (n=…)	Placebo (n=…)	Talc slurry	Placebo	Treatment effect (talc vs placebo) and 95% CI	P-value
Pleurodesis success at 5 weeks* (primary outcome) – no. (%)						
Pleurodesis success at 10 weeks* – no. (%)						
Pleurodesis success at 5 weeks* (defined by total fluid drained over two weeks) – no. (%)						

Pleurodesis success at 10 weeks* (defined by total fluid drained over two weeks) – no. (%)						
Further pleural procedures up to 10 weeks* - no. (%)						

*Treatment effects are hazard ratios

5.3.3 Table 3 – Results for secondary outcomes

	Number included in analysis		Summary measure			
Outcome	Talc slurry (n=…)	Placebo (n=…)	Talc slurry	Placebo	Treatment effect (talc vs placebo) and 95% CI	P-value
All-cause mortality up to 10 weeks* – no. (%)						
Disease-related mortality up to 10 weeks – no.(%)						
Non disease-related mortality up to 10 weeks – no. (%)						
Total volume of pleural fluid drained up to 10 weeks – mean (SD)						
Hospital inpatient bed days** – mean (SD)						
Thoracic pain*** – mean (SD)						
14						
28						
42						
56						
70						
Breathlessness*** – mean (SD)						
14						
28						
42						
56						
70						
EQ-5D*** – mean (SD)						
14						

28						
42						
56						
70						
QLQ-C30*** – mean (SD)						
14						
28						
42						
56						
70						
Overall size of pleural effusion						
Degree of septation of pleural fluid						
Adverse events* – no. (%)						
Serious adverse events* – no. (%)						

*Treatment effects are odds ratios

**Treatment effects are rate ratios

***Treatment effects are difference in means

6. REFERENCES

1. Kahan BC, Morris TP. Improper analysis of trials randomised using stratified blocks or minimisation. Stat Med. 2012;31(4):328-40. Epub 2011/12/06.
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3. Kahan BC, Morris TP. Assessing potential sources of clustering in individually randomised trials. BMC Med Res Methodol. 2013;13(1):58. Epub 2013/04/18.
4. White IR, Thompson SG. Adjusting for partially missing baseline measurements in randomized trials. Stat Med. 2005;24(7):993-1007. Epub 2004/12/01.

Section 2c – Summary of changes to analysis plan

- Removal of planned interim analysis
    - Version 1.0 of the statistical analysis plan stipulated that an interim analysis for efficacy be performed after 100 patients had been recruited, using the O'Brien-Fleming stopping rule for the primary endpoint. This stopping rule required a significance threshold for the primary outcome of 0.048 at final analysis. However, because patient recruitment was quicker than anticipated, the TSC felt that by the time data would be ready for the interim analysis (i.e. after the follow-up was complete for the 100^{th} patient, and the primary outcome had been adjudicated by two independent clinicians), the overall sample size target of 154 patients would be almost completed, rendering an interim analysis unnecessary. Therefore, the IDMC and TSC recommended that the interim analysis not be undertaken, and that the significance threshold for the final analysis be set at 0.05. This change was implemented to the trial protocol in version 6.0 (9/9/16), as part of substantial amendment SA7 (approved 7/10/16).