TIME1

The First Therapeutic Intervention in Malignant Pleural Effusion Trial (TIME1)

A 2 x 2 factorial trial to assess whether non-steroidal anti-inflammatory analgesics and small bore chest tubes are less painful than opiate analgesics and a large bore chest tubes in pleurodesis for malignant pleural effusion.

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Authorised by:

Name: Dr N Rahman
Role: Chief Investigator
Signature: 
Date: 20/02/2013
GENERAL INFORMATION

This document describes the TIME1 (The First Therapeutic Interventions in Malignant Effusion) 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 drafting, but corrections or amendments may be necessary. Clinical problems relating to this trial should be referred to the relevant Chief Investigator.

- Compliance
  This trial will be conducted in compliance with this protocol, Good Clinical Practice Guidelines and the Data Protection Act.

- Authorisation

- Sponsor
  This trial is being sponsored by the University of Oxford

Main Contacts

Chief Investigator, Trial co-ordinator and Principal Investigator for Oxford
Dr NM Rahman,
UKCRC Oxford Respiratory Trials Unit
Respiratory Medicine
Churchill Hospital
Old Road
Headington Oxford, OX3 7LJ
Tel: 01865 225227 Fax: 01865 857109

Principal Investigators for Recruiting Sites

Dr Justin Pepperell
Consultant Physician
Taunton and Somerset Hospital
Mugrove Park Taunton Somerset TA1 5DA
Tel: 01823 344635 Fax: 01823 343709 E-mail: justin.pepperell@tst.nhs.uk

Dr Frank Ryan
Vancouver Hospital and Health Sciences Centre
Division of Respiratory Medicine
The Lung Centre, 7th Floor, Gordon and Leslie Diamond Health Care Centre
2775 Laurel Street Vancouver, BC V5Z 1M9, Canada
Tel: 604 875 5710 Fax: 604 875 4695 E-mail: fryan@interchange.ubc.ca
Dr Alex West  
Department of Respiratory Medicine  
Medway District Hospital  
Windmill Road  
Gillingham, Kent ME7 5NY  
Tel: 01634 825215

Dr Andrew Leonard  
Department of Respiratory Medicine  
Conquest Hospital  
The Ridge,  
St Leonards-on-Sea,  
East Sussex, TN37 7RD  
Tel: 01424 755255

Dr Anoop Chauhan  
Respiratory Centre  
Trafalgar Building  
Queen Alexandra Hospital  
Portsmouth, PO6 3LY  
Tel: 023 9228 6665

Dr Jon Miles  
Department of Respiratory Medicine  
North Manchester General Hospital  
Delaunays' Road  
Crumpsall, M8 5RB  
Tel: 0161 795 4567

Dr Nabeel Ali  
Department of Respiratory Medicine  
Kingsmill Hospital  
Sutton in Ashfield  
Nottingham, NG17 4JL  
Tel: 01623 622515

Dr Andrew Bentley  
Department of Respiratory Medicine  
Wythenshawe Hospital  
Southmoor Road  
Manchester, M23 9LT  
Tel: 01612 915079

Dr Alina Ionescu  
Royal Gwent Hospital  
Cardiff Road  
Newport, NP20 2UB  
Tel: 01633 234234
Dr Stephen Fowler  
Consultant Chest Physician  
Lancashire Teaching Hospitals  
Royal Preston Hospital  
Sharoe Green Lane  
Fulwood  
Preston  
Tel: 01772 523237  
PR2 9HT  
Fax: 01772 522810

Dr Dipak Mukherjee and Dr Johnson Samuel  
Basildon University Hospital  
Nethermayne  
Basildon  
Essex  
SS16 5NL

Dr Tarek Saba  
Blackpool Victoria Hospital  
Whinney Heys Road  
Blackpool  
Lancashire  
FY3 8NR

Dr Ken Y. Yoneda, MD  
Associate Professor of Medicine  
Div. of Pulmonary and Critical Care Medicine  
4150 V Street, Suite 3400  
Sacramento, CA 95817  
Tel: 001 (916) 734-3935  
Fax: 001 (916) 734-7924  
UC Davis Medical Center

Dr Richard Teoh  
Consultant Physician  
Department of Respiratory Medicine  
Castle Hill Hospital  
Castle Road  
Tel: 01482 623083  
Cottingham  
Fax: 01482 623255  
North Humberside, HU16 5JQ

Dr Lee Dowson  
Consultant in Respiratory Medicine  
McHale Centre  
Royal Wolverhampton Hospital NHS Trust  
Wednesfield  
Wolverhampton  
Tel: 01902 694106  
WV10 0QP  
Fax: 01902
Trial Management

Emma Hedley (Clinical Trials Manager)
UKCRC Oxford Respiratory Trials Unit
Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford OX3 7LJ
Email: emma.hedley@orh.nhs.uk

Tel: 01865 225205
Fax: 01865 857109

Nicky Crosthwaite & Bethan Hughes (Research nurses)
UKCRC Oxford Respiratory Trials Unit
Respiratory Medicine
Churchill Hospital
Old Road
Headington
Oxford OX3 7LJ
Email: nicky.crosthwaite@orh.nhs.uk
bethan.hughes@orh.nhs.uk

Tel: 01865 225205
Fax: 01865 857109
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KEY:

NSAID=NON-STEROIDAL ANTI-INFLAMMATORY DRUG
1. SUMMARY

1.1 Lay summary

Patients with cancer that has spread (metastasised) often have fluid collecting around the lung as a result of cancer cells spreading to the membranes adjacent to the lung (malignant pleural effusion). This problem affects more than 200,000 patients per year in the UK and USA combined. The standard way of treating this condition, which may cause unpleasant symptoms such as breathlessness and cough, is to drain the fluid off and then seal the cavity, using a drug (talc) given into the chest drain. Talc causes inflammation in the lining of the lung and chest wall, sticking the two surfaces together and preventing fluid from recurring. This procedure is often very painful; the pain may be partly related to the size of the chest tube used and the type of analgesia taken by the patient during the procedure. Reducing the amount of pain associated with this procedure would be a substantial benefit for patients undergoing this procedure.

This trial is looking at which of two different drug regimens is more effective in preventing pleurodesis pain, and whether the size of chest tube influences pain. It will also address whether either of these influences success rate of pleurodesis.

1.2 Abstract and summary of trial design

This protocol describes a randomised 2 x 2 factorial trial to assess whether use of an ibuprofen based analgesic regimen is more effective than an opiate based regimen in reducing post pleurodesis chest pain and whether small bore chest drains are less painful than large bore chest drains in pleurodesis. It will also assess whether either of these interventions is associated with a decrease in pleurodesis efficacy.

1.2.1 Type of design

A randomised 2 x 2 factorial trial consisting of a superiority comparison and a non-inferiority assessment.

1.2.2 Diseases / Patients Studied

Eligible patients will be referred to a respiratory physician for pleurodesis for malignant pleural effusion. This includes all patients with suspected malignancy admitted for thorascoscopic biopsy and pleurodesis. Consecutive patients who fulfil the inclusion criteria will be recruited.

The inclusion and exclusion criteria will be collected as part of routine clinical care. The PI or nominated member of the team will approach eligible patients to discuss the study. A patient information leaflet will be given and the PI or nominated member of the team will discuss with the patient the aims, design and potential risks of the study.
The participant will be given time (normally at least 24 hours) to consider the proposal and any questions. Anyone participating in the study will be required to give written informed consent.

**Inclusion Criteria**

1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis may be established by:
   a) Histologically proven pleural malignancy OR
   b) Typical features of pleural malignancy seen on direct vision during thoracoscopy OR
   c) Pleural effusion in the context of histologically proven cancer elsewhere
2. Expected survival more than 1 month
3. Written informed consent

**Exclusion criteria**

1. Age < 18 years
2. Primary lymphoma or small cell lung carcinoma
3. Patients who are pregnant or lactating
4. Inability to give informed consent
5. History of GI bleeding or of untreated peptic ulceration
6. Known sensitivity to Non-steroidal anti-inflammatory drugs (NSAIDs) / opiates/ Paracetamol
7. Hypercapnic respiratory failure
8. Known intravenous drug abuse
9. Severe renal or liver disease
10. Known bleeding diathesis
11. Warfarin therapy
1.2.3 Trial interventions

Eligible patients will be randomised in an equal ratio, using a central telephone service. All patients will be randomised to one of opiate or NSAID based analgesic regimen. Only patients without thoracoscopy will also be randomised to receive a large bore chest drain or a small bore chest drain.

All participants in the trial will be administered regular background analgesia in the form of paracetamol 1g qds from the beginning of the trial until chest tube withdrawal. In addition, all participants will receive an anti-emetic (Metoclopramide 10mg or Cyclizine 50mg) on an as needed basis given the known side effect profiles of the study medications, to reflect normal clinical practise.

The NSAID based analgesic regimen consists of ibuprofen 800mg po tds to a maximum of 2.4g per 24 hours. The opiate based analgesic regimen consists of oral morphine initially at 10mg qds, which may be escalated to 20mg qds to a maximum of 80mg per 24 hours if pain is not well controlled. The opiate will be given in the form of oramorph (10mg / 5mls). Patients may refuse regular medication if they are not in pain.

Patients not adequately treated with these regimens will always have access to rescue analgesia as required (in the form of intravenous morphine). The treatment will continue from pleurodesis (day 0) to tube removal.

There is no standard analgesic regimen proven to be efficacious in preventing pain from pleurodesis, hence there is no “standard of care”, although the large bore chest drain and opiate based analgesic regimen is in line with current standard worldwide practise for pleurodesis in malignant pleural effusion and acts here as the “control” arm for the study.

1.2.4 Outcome Measures

The primary endpoints are:
- The average pain score whilst the chest drain is in situ up to 5 days
- Pleurodesis failure at 3 months post randomisation

The secondary endpoints include:
- Change in pain over time, efficacy measures, surrogate outcomes and adverse events (see section 9.2 for further details)

1.2.5 Duration

Participants in the study will be admitted for their chest drain and pleurodesis, in line with standard care. All chest drains will remain in situ for at least 48 hours post pleurodesis and removed at the clinician’s discretion. Pain scores will be taken at 8am, 12pm, 4pm and 8pm until the drain is removed from participants. Participants will be followed up at 4 weeks, 12 weeks and 6 months (to assess effusion recurrence) and until death via the Office of National Statistics.
1.2.6 Data recorded directly on CRFs

Data will be recorded on case report forms (CRFs), and sent to the Oxford Respiratory Trials Unit for data entry.

1.2.7 Ancillary studies / Sub studies

Patients in the TIME1 trial will additionally take part in the following sub studies:

1. An assessment of factors (including radiological) which predict pleurodesis success in malignant pleural effusion (Oxford patients only)
2. A study into whether use of pleural Ultrasound during day 0-3 can predict pleurodesis success (loss of visceral pleural movement) (Oxford patients only)
3. Prospective cohort study of toxicity due to graded talc.
4. Contribute toward the tissue and genetic library of patients with pleural disease held at the Oxford Respiratory Trials Unit
1.3 Flowchart

**Figure 1**: trial entry, randomisation, treatment and follow up

**Trial Entry**
Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis:
1. Histologically proven pleural malignancy
2. Typical features of pleural malignancy seen on direct vision during thoracoscopy
3. Pleural effusion in the context of histologically proven cancer elsewhere

Written informed consent
Expected survival more than 1 month

**NON-THORACOSCOPIC RANDOMISED**
- Large drain + Opiate
- Large drain + NSAID
- Small drain + Opiate
- Small drain + NSAID

**THORACOSCOPIC RANDOMISED**
- Opiate
- NSAID

***Drain removal and discharge when clinically appropriate***

Follow-up at 1, 3 and 6 months – average pain score whilst the drain remains in situ / pleurodesis failure at 3 months / CXR / thoracic USS / clinical Review

Follow up for 12 months
2. BACKGROUND

2.1 Introduction

Burden of Malignant Pleural Disease

Malignant pleural effusion is a common clinical problem and is increasing with a rising number of cases of carcinoma in an ageing population. With increased life expectancy and at current rates of malignancy, an extra 100,000 cases of cancer are expected per year by 2025\(^1\). Mesothelioma is an important cause of malignant pleural effusion, and is also increasing. In the UK, the rate of mesothelioma is predicted to increase until 2020\(^2\), with an estimated 65,000 patients dying of this disease between 2001 and 2050\(^3\). There are an estimated 300,000 new cases of malignant pleural effusion in the UK and USA per year\(^4,5\), translating to 1 new case per 1,000 population per year. In the UK, an average General Hospital will therefore see an estimated 250 new cases of malignant pleural effusions per year.

The majority of these patients will encounter unpleasant symptoms as a result of their malignant pleural effusion, such as breathlessness, chest pain or lethargy\(^6\). Removal of pleural fluid by thoracocentesis or intercostal drainage usually alleviates such symptoms. However, the majority of malignant pleural effusions will recur after a single drainage and so pleurodesis is advised\(^7\). The patient is therefore required to frequently attend hospital for therapeutic procedures, decreasing quality of life.

Pleurodesis offers these patients permanent control of pleural fluid and therefore avoidance of future related symptoms. Pleurodesis has reported success rates of between 60\%\(^8\) and 90\%\(^9\).

The procedure of pleurodesis is generally accepted to be one of the most painful common medical procedures. This is caused by two factors; firstly by the pleurodesis agent itself (sterile talc) inducing inflammation in the parietal pleura, and secondly the presence of a chest drain for fluid drainage. Although chest drain insertion and pleurodesis are commonly conducted procedures, there are very few studies addressing pain and analgesia in this context. One study of 26 patients suggested that insertion and presence of an indwelling chest drain is associated with high levels of pain and anxiety\(^10,11\), whilst a further study of 18 patients, replicated 2 years later, found that the majority of patients with a chest drain in situ experience persistent pain and discomfort\(^12,13\).

Chest Drain Size

The size of chest drain for optimal pleurodesis, in terms of pleurodesis success and comfort to patient, has not been addressed in any good quality studies. It is assumed that larger chest tubes cause more discomfort to the patient\(^14\), but it is also suggested that larger drains may be clinically more effective through achieving better drainage.
This aspect of pleurodesis has not been adequately studied and since this therapy is used in hundreds of thousands of patients per year, such poor evidence is unacceptable.

There are many case series suggesting that small bore (less than or equal to 14 French) chest drains are successful when used for pleurodesis in malignant pleural effusion\textsuperscript{15-27}. However, only five of these trials are prospective\textsuperscript{28-32} and the numbers in each individual study is relatively small. The only randomised study in this group was designed to assess relative efficacy of two different sclerosants and all patients received small chest drains\textsuperscript{33}.

There are only 3 studies directly comparing small and large bore chest drains\textsuperscript{34-36}, only one of which is randomised (Clements\textit{sen et al})\textsuperscript{37}. Although equivalent pleurodesis success was demonstrated in these trials, the Clementsen contained only 18 patients\textsuperscript{38}, while the two non randomised studies included 20\textsuperscript{39} and 102 patients\textsuperscript{40} respectively. Smaller chest tubes were found to be more comfortable than larger chest tubes\textsuperscript{41} in the Clementsen study, although these numbers are inadequate to address the questions of discomfort or pleurodesis success with sufficient power. Furthermore, accepted measures of pain assessment were not used.

Despite these many case series, the largest survey conducted of pleurodesis practise throughout the world\textsuperscript{42} found the majority of pleurodeses for malignant pleural effusion are conducted using 28 to 32F chest tubes. Only 14% of respondents to the survey preferred using a 14 to 18F chest tube\textsuperscript{43}. A large proportion of UK chest physicians are now using smaller bore chest drains for pleurodesis since in small case series smaller tubes are more comfortable and better tolerated\textsuperscript{44}. However, a study assessing associated problems with chest tubes inserted by chest physicians in the USA found a higher percentage of complications from small bore chest tubes (36%) than from large bore chest tubes (9%), although the number of small bore tubes inserted was far smaller (11 vs. 115)\textsuperscript{45}.

**Pleurodesis and Analgesia**

Pleurodesis is recognised to be a painful procedure\textsuperscript{46}, with rates of chest pain varying from 7% to 40% according to the sclerosant used\textsuperscript{47,48}. Despite the high incidence of often severe pain in this common procedure\textsuperscript{49,50}, analgesia, premedication and sedation are poorly studied for pleurodesis. As treatment of malignant pleural effusion is essentially palliative, it is of importance to give specific emphasis to preventing unpleasant symptoms wherever possible, perhaps especially relevant to those induced by medical treatments.

There is no standard analgesic regimen known to be effective in pleurodesis. The majority of physicians use opiates if pain occurs, given the often very painful nature of the procedure and the perception that opiate analgesia is the most potent form of analgesia. However, opiates have potential side effects, including respiratory depression, which is of particular importance in patients with respiratory compromise due to pleural effusion.
This is particularly important as many patients with malignant effusion are frail and elderly, increasing the risk of opiate toxicity.

Non-steroidal anti-inflammatory drugs (NSAIDs) are highly effective analgesics, and the randomised trial evidence of their use in post-operative pain suggests that they are substantially more effective than opiates\textsuperscript{51}. The magnitude of this benefit is emphasised by the large therapeutic advantage for pain relief associated with nonsteroidal therapy in meta-analysis of randomised trials. The most effective agent for the relief of acute post-operative pain is Ibuprofen 800mg (number needed to treat to achieve a 50\% reduction in total pain score = 1.6 vs. im morphine 10mg = 2.9)\textsuperscript{52}.

Pleurodesis produces pain of a similar magnitude to surgery and so NSAIDs may also be a better analgesic choice than opiates in this setting. However, there is also some caution influencing the use of NSAIDs in pleurodesis, as it is believed that they may decrease the efficacy of the pleurodesis itself through the drug’s anti-inflammatory actions. Only one published paper supports this theory\textsuperscript{53}, using data from a pig model. In this study, 10 pigs underwent mechanical pleural abrasion, with half the animals given NSAID (diclofenac 2mg / kg) for 3 weeks after the procedure until sacrificed. Pleurodesis success was assessed macroscopically and microscopically, and although macroscopically there was a significant difference in “pleurodesis score”, the difference microscopically did not achieve significance\textsuperscript{54}. However, there is no data in human subjects to support this view, very few animals were used and the NSAID regimen was given for far longer than would normally be needed to control the acute pain of pleurodesis. Furthermore, although there were less macroscopic adhesions in the pigs taking NSAIDs, this endpoint is not clinically validated as being equivalent to pleurodesis failure in the context of malignant pleural effusion.

Therefore, although clinical data on the question is lacking, NSAIDs have been avoided in pleurodesis despite being potentially the most effective agent in acute pain. Patients may therefore be suffering pain during pleurodesis unnecessarily and furthermore, when given opiates, may be exposed to dangerous side effects. Secondly, the important question of whether a large or small bore chest drain causes less discomfort has not been directly addressed. Furthermore, although it is assumed that pleurodesis success rates are similar regardless of tube size, this has not been directly tested. It may be that a larger bore chest drain facilitates chest drainage and therefore increases the likelihood of visceral and parietal pleural apposition and therefore pleurodesis success.

There are well validated systems of assessing acute pain and response to analgesia, which are easily measured using visual analogue scales (VAS)\textsuperscript{55} and the number needed to treat difference between high dose NSAID and opiate is large enough that a treatment effect should be detectable with an achievable sample size. Effectively and practically answering this question will immediately translate into improved patient care.
2.1.1 Population

Patients with a malignant pleural effusion requiring pleurodesis.

Inclusion Criteria
1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis may be established by one of:
   a) Histologically proven pleural malignancy OR
   b) Typical features of pleural malignancy seen on direct vision during thoracoscopy OR
   c) Pleural effusion in the context of histologically proven cancer elsewhere
2. Expected survival more than 1 month
3. Written informed consent

Exclusion criteria
1. Age < 18 years
2. Primary lymphoma or small cell lung carcinoma
3. Patients who are pregnant or lactating
4. Inability to give informed consent
5. History of GI bleeding or of untreated peptic ulceration
6. Known sensitivity to non-steroidal anti-inflammatory drugs (NSAIDs) / opiates / paracetamol
7. Hypercapnic respiratory failure
8. Known intravenous drug abuse
9. Severe renal or liver disease
10. Known bleeding diathesis
11. Warfarin therapy

2.1.2 Interventions

Analgesia

All participants in the trial will be administered regular background analgesia in the form of paracetamol 1g qds from the beginning of the trial until chest tube withdrawal.

The NSAID used for the purposes of this trial is Ibuprofen 800mg tds, at the recommended maximum dose of 2.4g per day. It is licensed for use in acute pain, and data from meta-analyses of acute pain suggest that a single dose of Ibuprofen 800mg is safe and more effective than opiates in reducing pain of the type produced by pleurodesis.

The opiate for the purposes of this trial is oral Morphine, given at an initial dose of 10mg qds and escalating if needed to 20mg qds (maximum of 80mg per day).

All participants will be prescribed an anti-emetic (e.g. Metoclopramide or Cyliczine) on a prn basis. Patients who are already on steroids are encouraged to take a proton pump inhibitor in addition to any anti-emetic according to local policy.
Chest Drains

The chest drains used will be a "small drain" (defined as 12F) and a "large drain" (defined as 24F). The insertion technique (seldinger, dissection, USS guided) will be recorded but is not specified.

2.2 Rationale and Objectives

a) To evaluate the efficacy of a non-steroidal based regimen in decreasing post pleurodesis pain as compared to an opiate based regimen.

b) To evaluate whether chest drain size influences amount of pain, post pleurodesis.

2.3 Relevant Studies / Trials

Background literature is reviewed in section 2.1.

2.4 Risks and Benefits

Non-steroidal anti-inflammatory drugs are very widely used as an analgesic. They are generally safe, although may cause gastro-intestinal erosions, GI bleeding, renal failure and exacerbate heart failure. Many of these effects occur when used over a period of months, which does not apply to this trial.

Opiates are also a widely used analgesic. They are generally safe, although may cause respiratory depression, decreased conscious level and constipation.

The trial will inform the standard of care for pleurodesis and prevent pain in this common procedure. Furthermore, the adverse event profile of the drug proven to be less effective can be avoided. This will be directly relevant to the treatment of more than 200,000 patients each year in the UK and USA.

Chest drain insertion is generally safe. It has a recognised set of complications including introduction of infection (1 in 500), bleeding and pain. Patients with malignant pleural effusion will require a chest drain as part of their routine care, and therefore the trial does not necessitate an extra procedure. Although larger chest drains may cause more discomfort on insertion, this is not tested and that is the reason for this trial. The complication rates of large versus small bore chest drain insertion are not known to be different. Insertion of chest drains as part of routine care involves use of local anaesthetic with its minor attendant risks.
3. SELECTION OF CENTRES / CLINICIANS

This study is a multi-centre study, with the Oxford Centre for Respiratory Medicine as the main recruiting centre. Other regional centres will recruit to the trial in which there are respiratory physicians with an interest in pleural disease and a track record of recruitment for clinical trials. The appropriate ethical and regulatory approval will be sought in all recruiting centres.

4. SELECTION OF PATIENTS

4.1 Patient Inclusion Criteria

1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis is be established by at least one of the following:
   a) Histologically proven pleural malignancy OR
   b) Typical features of pleural malignancy seen on direct vision during thoracoscopy OR
   c) Pleural effusion in the context of histologically proven cancer elsewhere
2. Written informed consent
3. Expected survival more than 1 month

4.2 Patient Exclusion criteria

1. Age < 18 years
2. Primary lymphoma or small cell lung carcinoma
3. Patients who are pregnant or lactating
4. Inability to give informed consent
5. History of GI bleeding or of untreated peptic ulceration
6. Known sensitivity to Non-steroidal anti-inflammatory drugs (NSAIDs) / opiates / paracetamol
7. Hypercapnic respiratory failure
8. Known intravenous drug abuse
9. Severe renal or liver disease
10. Known bleeding diathesis
11. Warfarin therapy

4.3 Number and source of patients

It is planned to enrol 320 patients from a number of centres. Please see section 9.1 for further details.
4.4 Screening Procedure

All patients with malignant pleural effusion requiring pleurodesis and all patients undergoing thoracoscopy for likely malignancy who fulfil the inclusion / exclusion criteria will be screened. A screening log will be kept documenting reasons for non-inclusion in the trial.

5. RANDOMISATION AND ENROLMENT PROCEDURE

Participants will be identified for the study according to the inclusion criteria. A member of the trial team will explain the trial to the patient and leave them with written information. After consideration, subjects who agree to take part will sign the consent form and the trial team will fill in an enrolment and randomisation form, acquiring a randomisation number.

Eligible patients will be randomised in an equal ratio, using a central telephone service. Randomisation will be done using minimisation by the following criteria:

a) Histological tissue type (mesothelioma vs. non-mesothelioma vs. unknown)

b) Thoracoscopic procedure (thoracoscopy pleurodesis vs. non-thoracoscopy pleurodesis)

c) Centre of recruitment

Patients without thoracoscopy will be randomised to receive one of:

1. Large bore chest drain (24F) + opiate based analgesic regimen
2. Small bore chest drain (12F) + opiate based analgesic regimen
3. Large bore chest drain (24F) + NSAID based analgesic regimen
4. Small bore chest drain (12F) + NSAID based analgesic regimen

Patients with thoracoscopy will be given a large bore chest drain (24F) and randomised to one of:

1. opiate based analgesic regimen
2. NSAID based analgesic regimen

The investigators and patients cannot be blinded to the different modes of treatment (large vs. small bore drain, Ibuprofen po vs. Morphine po) for practical reasons.
6. TREATMENT OF PATIENTS

6.1 Introduction

All participants in the trial will be administered regular background analgesia in the form of Paracetamol 1g qds from the beginning of the trial until chest tube withdrawal.

For patients allocated to NSAID analgesia will be given in the form of Ibuprofen 800mg orally tds to a maximum of 2.4g. If pain continues despite maximum trial medication, breakthrough analgesia will be permitted.

For those allocated to Opiate analgesia will be given in the form of oral morphine, initially at a dose of 10mg qds escalating to 20mg qds if needed, to a maximum of 80mg daily for the duration of the drain being in situ. If pain continues despite maximum trial medication, breakthrough analgesia will be permitted.

6.2 Accountability

Both analgesic products are in widespread clinical use for this indication and licensed for the treatment of acute pain. They will therefore be dispensed and administered by ward nursing staff in the same manner as other drugs, hence there will not be any additional drug accountability procedures other than what is routinely practised in the ward. Both small and large bore chest drains are in widespread clinical use for this indication. An operator experienced in both insertion techniques will insert all drains for the purposes of this study.

6.3 Measures of Compliance / Adherence

Compliance will be audited by completion of the trial forms and validation of the patient drug charts. The therapies for this trial will be given for the duration of chest drainage, such that complex compliance monitoring will not be needed. Use of breakthrough analgesia will be confirmed by the drug chart.

6.4 Non-trial Treatment

6.4.1 Medications permitted

Medications

Participants in the trial may receive all other normal treatment, with the exception of analgesics. All analgesic medications must be stopped at least 24 hours prior to pleurodesis. Use of a proton pump inhibitor according to local guidelines is encouraged, at the discretion of the physician.

If the trial medication (Ibuprofen po or Morphine po) does not adequately cover pain after 1 hour, patients will have free access to rescue medication, this being Morphine 10mg iv, im, or sc (up to 1 hourly).
All patients undergoing talc pleurodesis for malignancy will be given prophylactic heparin.

No patients are to be discharged on NSAIDS, regardless of which arm of the trial they are in.

**Chest Drains**

Chest drains will be managed as per a standardised protocol, with a suction schedule for both large and small drains, and sterile flushes for small drains only. Patients undergoing thoracoscopy will be randomised to drug only, as the size of port used during thoracoscopy requires a large bore chest drain.

Drains will be sutured to the skin in all cases, to prevent drain displacement and to equalize any pain from drain stitches in all groups. If a drain is displaced accidentally, the need for re-insertion will be dictated by clinical situation. The 4 hours after drain re-insertion will not be used in analysis of average pain score, although pain VAS will be measured.

**6.4.2 Medications Not Permitted**

No other analgesic apart from that described in the study medication and breakthrough regimen is allowed from trial entry to tube withdrawal post pleurodesis (i.e. regular Paracetamol plus assigned study analgesia plus breakthrough medication only). This includes opiate slow release patches.

**6.4.3 Data on Concomitant Medication**

No concomitant analgesics are permitted but the use of previous analgesia will be recorded, as well as reasons, specifically whether analgesia was used for pain thought to be caused by this presentation of pleural disease.

**6.4.4 Co-Enrolment Guidelines**

Patients should not be enrolled in any other clinical studies during the period from pleurodesis to chest tube withdrawal. After this period, participants are free to participate in other trials, excluding those involving further pleural procedures or analgesia trials for a period of 3 months.
7. ASSESSMENTS AND PROCEDURES

7.1 Flow chart for trial schedule

<table>
<thead>
<tr>
<th>Trial Entry</th>
<th>Randomisation</th>
<th>Chest drainage / pleurodesis</th>
<th>Interventions</th>
<th>Post pleurodesis</th>
<th>Day of tube removal</th>
<th>Follow up 1, 3 and 6 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malignant pleural effusion requiring drainage / pleurodesis OR Thoracoscopic diagnosis of malignancy likely Baseline chest pain score and pain visual analogue scale (VAS) Baseline blood tests (FBC / U+E / LFTs) Baseline ABG Pleural fluid biochemistry + pH Blood and pleural fluid for storage Pre-treatment USS (Oxford patients only)</td>
<td>Complete Randomisation and Enrolment Form Randomisation to one of the intervention regimes (next column) Stratified/Minimised by 1. Histological tissue type (mesothelioma vs non-mesothelioma vs unknown) 2. Thoracoscopy vs non-thoracoscopy 3. Centre</td>
<td>Drain insertion / thoracoscopy using standard premedication (2-5mg midazolam iv + up to 20mls 2% lignocaine topically) Pleurodesis = 4g sterile high grade talc Standard premedication for non-thoracoscopy pleurodesis: ● 2mg midazolam iv + up to 20mls 2% lignocaine topically OR ● 2 mg midazolam iv + 30mls 0.125% bupivacaine intrapleurally</td>
<td>Large bore chest drain (24F) + morphine 10-20mg po 6 hourly Small bore chest drain (12F) + morphine 10-20mg po 6 hourly Large bore chest drain (24F) + ibuprofen 800mg 8 hourly Small bore chest drain (12F) + ibuprofen 800mg 8 hourly</td>
<td>VAS pain score taken at 8am, 12pm, 4pm and 8pm (qds in total) Breakthrough analgesia prn (morphine 10 mg iv / im) Time to remedication ABG 48 hours post pleurodesis Daily FBC / U+E QDS observations Blood and pleural fluid for storage Thoracic USS (Oxford patients only) Continuous oximetry (Oxford patients only) including overnight oximetry</td>
<td>Tube removal Primary endpoint = average pain while drain in situ up to 5 days Report adverse events Thoracic USS (Oxford patients only) Thoracic USS (Oxford patients only)</td>
<td>Average pain score CXR</td>
</tr>
</tbody>
</table>
7.2 Procedures for assessing efficacy

<table>
<thead>
<tr>
<th>Enrolment / Randomisation</th>
<th>Patient information leaflets standardised to ensure one form of analgesia is not suggested to be better than another Standard protocol (sedation / technique) for drain insertion and pleurodesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1 to day of drain removal</td>
<td>Nursing SOPs to elicit VAS in standardised way</td>
</tr>
<tr>
<td>4 week follow up</td>
<td>Any patient with symptomatic breathlessness referred to Oxford Centre (to blinded assessor) as to whether further drainage warranted</td>
</tr>
<tr>
<td>12 week and 6 month follow up</td>
<td>As for 4 week follow up</td>
</tr>
</tbody>
</table>

7.3 Loss to follow up

Loss to follow up will be minimised by close liaison with the patient’s general practitioner and follow up at 4 weeks, 12 weeks and 6 months will be arranged at the Oxford Centre for Respiratory Medicine on patient discharge. All deaths will be recorded via the Office of National Statistics.

7.4 Trial closure

Trial closure will be at completion of final patient follow up (6 month post final randomisation), when it will be pre-planned or at the direction of the trial team.

8. WITHDRAWAL OF PATIENTS

8.1 Withdrawal from trial intervention

As the trial intervention occurs as an in patient over approximately 3 days, withdrawal from the trial is not anticipated during days 1 to day of drain removal post pleurodesis.

8.2 Withdrawal from the trial completely

For participants moving from the area, every effort will be made to continue follow up using telephone interviews with the patient, their GP and local hospital specialists. For patients withdrawing from the trial for other reasons, information collected will be used up to this point.
If further relevant information becomes available from routine follow up (i.e. non trial follow up), this may be used for the purposes of the study, as long as the patient consents to this.

9. STATISTICAL CONSIDERATIONS

9.1 Sample Size

Sample size calculations were performed for both primary outcomes (pain and pleurodesis failure), and the outcome that gave the largest sample size was used as the basis for this study.

**Analgesia and Pain**

The hypothesis that non-steroidal analgesia is superior to opiates for pleurodesis is supported by extensive randomised controlled data in acute pain. The sample size for this trial is calculated from Norholt et al, a randomised double-blind placebo controlled trial directly comparing non-steroidal analgesia to opiate in patients undergoing third molar dental extraction (lornoxicam 20mg iv vs. morphine 10mg iv vs. placebo). This model of acute severe pain is probably comparable to the pain intensity produced by pleurodesis. Pain was scored on a 5 point categorical verbal rating scale, which has been shown to closely approximate to a be a Visual Analogue Scale, the outcome assessment index used in this study. The Sum of Pain Intensity Difference (SPID) over 8 hours after medication was calculated for patient groups. The average pain relief score from non-steroidal use was 9.4 (SD 6.1) compared to 2.2 (SD 5.6) for opiate and -1.3 (SD 5.0) for placebo.

Based on the above trial; assuming 90% power, a 5% type I error rate, an effect size of 7.2 a standard deviation of 6.1 in each treatment group, and 10% loss to follow-up, 36 patients would be required. This has been rounded up to 40 patients.

The provision of background paracetamol analgesia for all patients may decrease the “pain signal”, although it is well recognised that paracetamol alone is inadequate analgesia for severe acute pain such as is seen in pleurodesis. However, the far larger recruitment number required for the pleurodesis efficacy question (second primary outcome) will ensure that the trial is not underpowered for the pain analysis.

**Drain size and Pain**

The second power calculation relates to drain size and pain. There are no randomised studies addressing pain differences between large and small bore drains to permit a power calculation to be conducted for the drain size and pain analysis. To define the relationship between chest tube size and chest pain, we conducted a retrospective observational study, to assess the results of a self administered categorical pain score administered to 123 patients taking part in a previous study in pleural infection (the MIST1 study). This is the largest set of prospective data comparing comfort in large versus small chest drains in a well defined cohort with a single disease. The pain score was administered during chest drain insertion, while the chest tube was in place and
during removal, and the scores summated to produce a summary score, which was compared in patients having smaller (<14F) and larger (>14F) drains (primary analysis). Larger drains were associated with more pain than smaller drains (large n=44, median pain score 7, IQR 5-8, small n=79, med 5, IQR 4-7, p=0.006, Mann-Whitney). This observational data suggesting small drains are less painful than large drains, achieved statistical significance with only 120 patients and using a less sensitive measure of pain (Categorical scale as opposed to VAS as proposed here). The total sample size of this randomized trial (320 patients) is therefore likely to be adequately powered to assess pain outcomes as related to drain size.

**Pleurodesis Efficacy**
The assessment of whether analgesic type or tube size affects pleurodesis efficacy, is designed as a non-inferiority study (with the large bore drain and opiate arm as the control group) Talc pleurodesis has a 20% failure at three months in the published literature\(^6\) and in our own unit (internal audit data). Assuming an acceptable margin of increase in pleurodesis failure of 15% (= d) (to 35%), 90% power, a one sided type one error rate of 5% and allowing for a 10% loss to follow up, 318 patients are required for analysis. This has been rounded up to 320 patients.

### 9.2 Outcome Measures

#### Primary outcomes

**Average pain score whilst the chest drain is in situ up to 5 days**
Pain will be measured using a Visual Analogue Score (VAS), on a 0-100mm scale (to
the nearest mm) and will include all randomised patients with at least one recorded VAS score post-randomisation. Patients will fill in four VAS scores per day at 8am, 12pm, 4pm, and 8pm. The average pain score will be calculated using all VAS measurements from randomisation until the drain is removed, up to a maximum of 5 days. Patients will be able to take rescue medication as needed, and will complete an extra VAS score prior to taking any rescue medication. Rescue medication will be accounted for by assuming the VAS score taken immediately prior to ingestion of rescue medication would have continued until the next scheduled VAS score (i.e. the next scheduled VAS score will be replaced by the score taken when rescue medication was used).

VAS will be measured by two independent observers, blind to treatment arm. If there is a difference in VAS score of 10% or less between the two observers, then an average of the two scores will be taken. If there is a difference of more than 10%, then the VAS score will be re-measured and differences will be resolved by discussion.

**Pleurodesis failure at 3 months**
The second primary outcome is pleurodesis failure at 3 months. Patients will be classified as a pleurodesis failure if they undergo further pleural intervention for relief of
breathlessness on the same side as their pleurodesis at anytime between randomisation and 12 weeks.

Patients will be referred for further pleural intervention if a chest x-ray shows 50% or more fluid as judged by the local investigator in association with symptoms. If a chest x-ray shows less than 50% fluid, then a patient can be referred for further pleural intervention if the attending clinician discusses the case with a second clinician who is blind to treatment arm, and they reach a consensus regarding further treatment.

Patients that die before 12 weeks post-randomisation will be considered as a success if no further pleural intervention was required prior to death.

**Secondary outcomes**

Secondary outcome measures include:

**Efficacy measures**
- Changes in pain over time
- Clinician’s assessment of whether further pleural procedure was required up to 12 weeks post-randomisation
- Time from randomisation to pleurodesis failure up to 6 months
- Pain scores at 4 and 12 weeks post-randomisation
- Volume of pleural fluid drained (mls) whilst the drain is in situ
- Number of times rescue medication was taken during hospital stay
- All-cause mortality up to 12 months
- Length of hospital stay (measured as time from randomisation until discharge)
- Area of chest radiograph pleural opacity at 4 and 12 weeks
- Number of patients for whom there is a complication in inserting the chest drain

**Surrogate outcomes**
- Change in haemoglobin (Hb) level from baseline to day 2
- Change in whitecell count from baseline to day 2
- Change in creatinine levels from baseline to day 2
- Change in albumin levels from baseline to day 2
- Change in ALT/AST levels from baseline to day 2
- Change in alkalinephosphate levels from baseline to day 2
- Change in CRP from baseline to day 2
- Change in Glasgow Coma score from baseline to day 2
- Change in urea from day of enrolment to hospital discharge

**Adverse events (AEs)**
- The proportion of patients that develop a fever (> 37.5 °C) from the day of pleurodesis to day 2 post pleurodesis.
- The proportion of patients who experience a severe reaction to talc pleurodesis
- The proportion of patients with a serious adverse event (SAEs)
9.3 Interim Monitoring and Analyses
An independent data monitoring committee (IDMC) will be established. Numbers of adverse events will be regularly monitored. If there is evidence of harm to one treatment arm, the IDMC will convene (by telephone or in person) to discuss. Only if there is highly significant evidence of substantial harm to one treatment arm will the trial be terminated (the exact stopping rules will be determined by the trial steering committee and agreed by the Data Monitoring Committee).

9.4 Analysis Plan
The first primary outcome, the average pain score whilst the chest drain is in situ up to 5 days, will be analysed by intention-to-treat (ITT), and will include all randomised patients with at least one recorded VAS score post-randomisation. The second primary analysis, pleurodesis failure, will be assessed for non-inferiority. Both an intention-to-treat (ITT) and a per-protocol (PP) analysis will be performed. The ITT analysis will include all randomised patients on whom a pleurodesis failure outcome is available and the PP analysis will include all randomised patients who had a chest drain inserted and received talc. All secondary outcomes will be analysed using ITT and will include all randomised patients on whom an outcome is available.

Only patients who do not undergo thoracoscopy will be randomised to a 24F or 12F drain, and so only non-thoracoscopy patients will be included in the primary comparison of drain sizes for each outcome. A secondary analysis will compare 24F to 12F drains and will include all thoracoscopy and non-thoracoscopy patients.

All outcomes will be analysed for superiority, with the exception of pleurodesis failure at 12 weeks. This will be analysed for non-inferiority, with a non-inferiority margin of 15%. For the non-inferiority comparison, the opiate group and the 24F group will be considered as the control. All superiority analyses will be two-sided, and considered statistically significant at the 5% level. The non-inferiority analysis for pleurodesis failure at 12 weeks will be assessed using a two-sided 90% confidence interval (which is equivalent to a one-sided test at the 5% level).

For both primary outcomes (pain and pleurodesis failure), an interaction test between drain size and analgesia will be performed at the 5% significance level, with no correction for multiple tests. These analyses will be ITT and will include all recruited patients. If a significant interaction is found for either outcome, then analysis for a four-arm trial will be performed for all outcomes. If the interaction test is not significant for either outcome, then a factorial analysis will be used for all outcomes.

The first primary outcome (pain) will be analysed using a mixed-effects linear regression model, with a random-effect for centre. For the second primary outcome, pleurodesis failure up to 12 weeks will be analysed using a generalised linear model with a binomial family and identity link.

All superiority analyses will be considered statistically significant at the 5% level. A full statistical analysis plan will be developed and signed off prior to database lock and any analysis.
10. DATA VERIFICATION AND SITE MONITORING

10.1 Monitoring at the Co-ordinating Centre and MRC/CTU
Data stored at the Co-ordinating Centre will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. If any such problems are identified, a photocopy of the problematic CRF(s) will be reviewed for checking and confirmation or correction, as appropriate – any data which are changed will be crossed through with a single line, initialled and dated.

10.1.1 Confidentiality
Full medical confidentiality will be preserved. The declaration of Helsinki is accepted as the basis for conducting this trial. Investigators at the recruiting centres shall sign an agreement agreeing to adhere to this protocol and stating their responsibilities. Participants personal ID will not be disclosed. Patients involved in this trial will be identified only by initials and trial number on all CRF’s. Stored specimens at Oxford will only identify patients by trial no. Patients will not be individually identified in any results publications.

10.1.2 Quality Assurance and Quality Control of Data
Quality Assurance
Due to the nature of the two interventions (chest tube size and analgesia), blinding of subject and investigator is not possible. Ethical and regulatory approval will be obtained as appropriate. A register of randomisable subjects will be kept in recruiting centres. Randomisation will be by a central randomisation service.

Quality Control
The data will be stored centrally in the trial database and subject to duplicate and range checks with arising queries resolved with CRFs. Data validation of primary data will include at least confirmation of informed consent, eligibility criteria and primary endpoint data. In addition all the data of 10% of participants will be source validated.

10.1.3 Direct Access to Source Documents
The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents to authorised auditors and monitors.

10.2 Safety Reporting

10.2.1 Definitions

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

10.2.3 Adverse Drug Reaction (ADR)

All untoward and unintended responses to a medicinal product related to any dose.

The phrase "responses to a medicinal products" means that a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

10.2.4 Unexpected Adverse Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg. Investigator's brochure or summary of product characteristics).

10.2.5 Serious or Severe Adverse Events

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

10.2.6 Serious Adverse Event or Adverse Drug Reaction

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death,
- Is life-threatening,

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the patient 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.

1. Requires inpatient hospitalisation or prolongation of existing hospitalisation,
2. Results in persistent or significant disability/incapacity, or
3. Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether an adverse event is serious in other situations.
10.2.7 Expected Adverse Drug Reactions

The following adverse reactions will be monitored in line with the known possible side effects of opiates and non-steroidals (specifically decreased conscious level / decreased respiratory rate (opiates) and gastrointestinal bleeding / renal dysfunction (NSAIDs). In addition, a small number of adverse reactions to talc are expected:

1. Any gastrointestinal bleeding. Requirement for fluid resuscitation, blood transfusion or a significant drop in blood pressure or haemoglobin level will be noted on adverse event forms.
2. New renal failure, or worsened renal function
3. Hypoxaemia with oxygen saturations <90%, requiring additional oxygen
4. Sustained decreased conscious level of > 1 hour between 8am and 12am
5. Drug and talc related adverse reactions

10.2.8 Expected Serious Adverse Events

Expected adverse events in this study include 20% mortality at 3 months from the underlying metastatic malignancy, as shown in previous internal audit data in patients with malignant pleural effusion. Expected death due to progression of known malignancy as judged clinically will therefore be reported on CRFs only, and the trial team will be notified of all deaths by the ONS flagging system.

All deaths occurring during the first 3 days post randomisation will be reported as serious adverse events in the usual way (i.e. SAE form to be sent to coordinating centre and sponsor to be notified within 1 working day of awareness of event).

Incidences of renal failure, GI bleeding and opiate toxicity are taken to be notable adverse events (NAEs), and will be reported as SAEs but do not require immediate reporting. NAEs will be reported on SAE forms but without the need to report to the co-ordinating centre within one working day of awareness (the form will be completed at the local centre and sent to the co-ordinating centre by post).

10.2.9 Causality Assessment

All cases judged by either a medically qualified health care professional as having a reasonable suspected causal relationship to the study medication qualify as ADRs.

10.3 Serious Adverse Event Reporting Procedures

A: Non Oxford Centre

When an SAE (other than an NAE) occurs in a non oxford centre the local PI informs the co-ordinating centre within 1 working day of awareness to discuss details of the SAE with the CI or the trial co-ordinator. This permits consideration of whether the event meets the definition of a SUSAR (ie related and unexpected). SUSARs are not anticipated in the context of this trial as the medication under investigation has been used in clinical practice for many years and the side effect profile is established and well known. An SAE form is completed by the local PI or designee and a copy of the SAE form is sent to the local R&D department and co-ordinating centre within 1 working day of awareness.
The CI or trial co-ordinator completes the clinical review section of the SAE form. A copy of the completed SAE form is sent to Clinical Trial and Research Governance (University sponsor representative) within 1 working day of arrival of the SAE form at the co-ordinating centre.

B: Oxford Centre
The process of SAE reporting is identical to that of non-oxford centres with the exception that the trial co-ordinator may not provide independent clinical review. This role is therefore conducted exclusively by the CI or designee (who would be an experienced chest physician – please see adverse event reporting SOP). For this purpose the trial co-ordinator acts as local PI.

10.3.1 SUSAR Reporting
A SUSAR will result in immediate contact with the trial statistician and MRC/CTU to consider the need for appropriate response (eg IDMC, TSC, etc).

Fatal or life threatening SUSARs must be reported to the MHRA and ethics committee within 7 days and all other SUSARs within 15 days. The co-ordinating centre will inform centres of relevant SUSARs which may adversely affect subject safety.

In addition to the expedited reporting above, the sponsor/CI shall submit once a year throughout the clinical trial or on request a safety report to the Competent Authority and Ethics Committee.

10.3.2 Role of MRC/CTU
MRC/CTU will have access to the trial database through the trial statistician. The trial statistician manages liaison with the IDMC, including arranging meetings and IDMC reports.

SAE forms are entered into the trial database (held at the MRC/CTU) at the earliest opportunity by remote data capture web link at the co-ordinating centre.

10.3.3 Timelines of Safety Reporting
All SAEs will be reported during the first 3 days post randomisation. It will be left to the investigator’s clinical judgment whether or not an AE is of sufficient severity to require the patient’s removal from treatment.

Subsequent to this, only NAEs (as defined above) will be reported as defined above.

SUSARs are reported at any time during the follow up period. Local PIs will assess whether an event is serious (by regulatory criteria), unexpected (by from the patients clinical history and the nature of the trial drug) and related to trial medication. In these circumstances the PI will make immediate contact through the 24 hour trial mobile with the co-ordinating centre to discuss whether a SUSAR has occurred and to precipitate appropriate responses. As explained above, SUSARs are not anticipated in this trial due to the side effect profile of the trial medication being well established.
11. ANCILLARY STUDIES

1. Participants recruited in the Oxford Centre for Respiratory Medicine will be asked to take part in an ultrasound based study, assessing whether pleural ultrasound characteristics on days 0 to 3 are able to predict pleurodesis success.

2. Participants will be asked to consent to other data from this trial being used to find predictors of pleurodesis efficacy (including radiological).

3. Participants will be asked to contribute toward the tissue and genetic library of patients with pleural disease held at the Oxford Respiratory Trials Unit

4. Data collected during the trial will be used to contribute to a prospective data set of toxicity induced by high grade talc

12. ETHICAL CONSIDERATIONS AND APPROVAL

12.1 Ethical considerations
There are no potentially difficult ethical considerations related to this trial.

12.2 Declaration of Helsinki
The Investigator will ensure that this study is conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

12.3 ICH Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in full conformity with relevant regulations and with the MRC Guidelines for Good Clinical Practice 1998.

12.4 Informed Consent
Written and verbal versions of Informed consent will be presented to the subject detailing no less than: the exact nature of the study; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the patient/subject is free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

The patient/subject will be allowed as much time as wished to consider the information, and the opportunity to question the Principal Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of subject dated signature, signature of the person who presented informed consent and, if different, the Principal Investigator (or named Co-Investigator). A copy of the signed informed consent will be given to the subject. The original signed form will be retained in the patient records, and a copy retained at the
study site in the trial site file.

12.5 Independent Ethics Committee
A copy of the protocol, proposed informed consent form, other written patient/subject information and any proposed advertising material will be submitted to an Independent Ethics Committee (IEC) for written approval.

The Investigator will submit and, where necessary, obtain approval from the IEC for all subsequent protocol amendments and changes to the informed consent document. The Investigator will notify deviations from the protocol or SAEs occurring at the site to the sponsor and will notify the IEC of these in accordance with local procedures.

12.6 Patient/subject Confidentiality
The Investigator will ensure that the subject’s anonymity is maintained. The subject will be identified only by initials and a subject ID number on the CRF. All documents will be stored securely and kept in strict confidence in compliance with the Data Protection Act.

13. REGULATORY APPROVAL
This trial has been given approval from the MHRA in the form of a CTA No: 21584/0215/001-0001.

14. INDEMNITY
Indemnity and/or compensation for negligent harm arising specifically from an accidental injury for which the University is legally liable as the Research Sponsor will be covered by the University of Oxford. The NHS will owe a duty of care to those undergoing clinical treatment, with Trust Indemnity available through the NHS Litigation Authority Scheme.

Indemnity and/or compensation for harm arising specifically from an accidental injury, and occurring as a consequence of the Research Subjects’ participation in the trial for which the University is the Research Sponsor will be covered by the University of Oxford.

15. PUBLICATION
The preparation of a manuscript for rapid publication will be the sole responsibility of the Trial Team. High priority will be given to this and it would be anticipated that a report will be completed within six months of a decision to stop the trial. No other publications, either in writing or verbally, will be made before the definitive manuscript has been agreed and accepted for publication, without the prior approval of the Committee.

All publications shall include a list of principal investigators, and named authors will include the trial’s Chief Investigator, Key Investigator(s), Statistician(s) and Trial Manager(s) involved.
16. TRIAL COMMITTEES

16.1 Trial Steering Committee (TSC)
The trial steering committee comprises of:

Dr Rob Miller – Independent Chairman
Dr Naj Rahman – Chief Investigator, Oxford PI/Trial Co-ordinator
Mrs Emma Hedley – Trial Manager
Mrs Nicky Crosthwaite and Miss Bethan Hughes – Trial Nurses
Professor Andrew Nunn – Trial Statistician
Dr Alex West – Key Investigator
Dr YCG Lee – Key Investigator
Dr Nick Maskell - Key Investigator
Dr Douglas Seaton - Independent Member

The TSC will meet to approve the trial protocol and as required thereafter. It will be responsible for supervision of the trial in all its aspects. It will be responsible for ensuring completion of the trial to clinical and GCP standards, for close of the trial (collaboration with the DMC as appropriate) and for timely final report preparation.

16.2 Data Monitoring Committee (DMC)
The data monitoring committee comprises of:

Professor Tim Peto – Chairman
Professor Maria Quigley – Independent Statistician
Dr Angela Crook – Trial Statistician (will also be present)
Professor Duncan Geddes – Independent Clinician/Member

The DMC will perform a review in collaboration with the TSC. It will consider the findings from other relevant studies. It will review safety data as required by the TSC (this is an un-blinded trial) and will convene as required at the request of the TSC communicating through the trial statistician.

17. PROTOCOL AMENDMENTS
Version 1.0 (Dated 09/12/2005)
Original version

Version 1.1 (Dated 10/04/2006)
Ethics approved version
Page 6 – paragraph 2 amended
Page 34 and 40 – Patient Information Sheet amended
Page 44 – Consent Form amended

Version 1.2 (02/05/2006)
Page 2 – Added trial managers – Nicky Crosthwaite and Emma Hedley
Page 5 – Secondary endpoints amended
Page 6 – Exclusion criteria and trial interventions amended
Page 7 – Outcome measures amended
Page 13 – Exclusion criteria and Interventions amended
Page 14 – Selection of Centres amended
Page 17 – Accountability amended
Page 18 – Medications amended
Page 20 – Flow chart amended
Page 21 – Trial closure amended
Page 22 – Outcome measures amended
Page 23 – 26 Data Verification and Site Monitoring expanded
Page 27 and 28 – Ethical Considerations and Indemnity expanded
Page 34 and 39 - Patient Information Sheets amended
Page 44 – Consent Form amended

Version 1.3 (12/12/2006)
Please see additional sheet.

Version 1.4 (25/07/2007)
Page 11 – section 1.2.3
Page 14 - section 2.1.2
Page 17 – section 5
Page 18 – section 6.4.1
Page 19 – section 6.4.2
Page 20 – section 7
Page 23 – addition of a new paragraph

Version 1.5 (29/11/2007)
Page 2/3 – Addition of new centres
Page 7 – section 1.2.3
Page 8 – Section 1.2.4
Page 9 – section 1.2.5 / 1.2.6
Page 10 – flowchart amended
Page 16 – section 4.3
Page 27 – section 10.2.7 / 10.2.8 / 10.3
Page 28 – section 10.3.1 / 10.3.2 / 10.3.3
Page 31 – section 16

Version 1.6 (26/08/2008)
Page 4 – Added new centres
Page 8 – section 1.2.2 Exclusion criteria point 12 has been deleted to include patients on current or recent corticosteroids.
Page 9 - Primary endpoints and flowchart, VAS questionnaire is measured 4 hourly during the day and not 6 hourly.
Page 16 & 20 - Section 2.1.2 and 6.4.1 addition of third paragraph.
Page 20 - Section 6.3 Amendment to paragraph
Page 26 - Section 9.3 Paragraph amended.
Page 29 - Section 10.2.7, 10.2.8, 10.3, 10.3.1, 10.3.3 Section amended in line with current guidelines.
Page 32 Section 12.4 & 15 Amended
Page 43 - Appendix 4 - Flowchart amended

Version 1.8 (06/01/2009)
Page 2 – New PI added
Page 4 – New PI added

Page 10 – section 1.2.3, 4th paragraph treatment will continue from pleurodesis to tube removal not day 3.

Page 13 & 20 – 1.3 flowchart and 6.1 4th paragraph treatment will be for the duration of the chest drain not for 3 days.

Page 20 – section 6.1, 3rd paragraph ibuprofen will be given tds not prn.

Page 21 – section 6.4.1 1st paragraph proton pump inhibitor is used at the discretion of the PI and not if the patient is on steroid therapy.

Page 21 – section 6.4.1 2nd paragraph morphine to be given IV, IM, SC. New sentence added to say that no patients should be discharged on NSAIDS.

Page 22 – section 6.4.2 & 6.4.4 medication and breakthrough meds are allowed until tube withdrawal and not at day 3.

Page 23 & 24 – 7 flowchart & 7.2 day 3 section amended to day of tube removal

Page 24 – section 8.1 day of chest drain removal and not day 3.


Page 27 – section 9.2 pleurodesis efficacy last paragraph added.

Page 27 – section 9.4 point 2 amended.

Page 34 – section 16.1 trial statistician changed from Andrew Nunn to Angela Crook and a new independent clinician/member added Professor Duncan Geddes

Page 41 – appendix 2 – added approximately 3 days for drug duration.

Version 1.8 (06/01/2009)
Page 4 & 5 Addition of new PIs.

Version 1.9 (25/03/2009)
Page 4 & 5 Addition of new PIs and change of PIs.

Version 2.0 (01/12/2009)
Page 4 Change of PI.

Version 3.0 (06/01/2011)
Page 2 Change of CI
Page 2-4 removal of non-participating centres details, update of trial team members
Page 34 change of TSC members
Front cover: Unit name change to UKCRC Oxford Respiratory Trials Unit

Version 3.1 (05/05/2011)
Page 11 admin error it is noted in point 2 that the second primary endpoint is pleurodesis success rate at 1 and 3 months, this in fact should only be 3 months.

Version 3.2 (05/09/2012)
Various amendments made throughout the protocol, mainly moving sections around to be more in line with final statistical analysis plan.

18.REFERENCES


APPENDIX 1

**Visual Analogue Pain Score**

**Visual analogue scales**

**Pain relief scale**

NO relief of pain  |  COMPLETE relief of pain

**Pain intensity scale**

LEAST possible pain  |  WORST possible pain

Calculation of TOTPAR 50:

Figure 9: Calculating TOTPAR and % maxTOTPAR
APPENDIX 2: LAY SUMMARY

THE TIME 1 TRIAL
LAY PERSON’S SUMMARY

Entry into the trial
Requires a clinically confident diagnosis of cancer spread to the lining of the lung (malignant pleural effusion) requiring drainage and pleurodesis (obliteration of the space where fluid collects by injecting sterile talc into the chest drain). This can be established by:
1. Cancer proven histologically in the pleura (i.e. seen under a microscope)
2. Typical features of pleural cancer seen at thoracoscopy (i.e. typical appearances seen with the naked eye when camera is inserted into the chest)
3. Fluid on the lung in the context of established and proven cancer elsewhere
Patients must provide written informed consent
Patients must be expected to survive for more than 1 month

ALLOCATED TO TREATMENT ARM AT RANDOM

Large bore drain + NSAID analgesia For ~3 days
Large bore drain + Opiate analgesia For ~3 days
Small bore drain + NSAID analgesia For ~3 days
Small bore drain + Opiate analgesia For ~3 days

Pleurodesis done on day 0
Drain removed ~day 3
Pain measured 4 times / day during days 1 to ~3
Discharge when clinically appropriate

Follow up
1, 3 and 6 months = Out patients for: clinical assessment, chest x-ray, Pain score

Outcome measures: Pain in 72 hours post pleurodesis, pain and fluid re-accumulation at 1, 3 and 6 months.
APPENDIX 3: CALCULATION OF TOTPAR

**Calculation of Total Pain Relief (TOTPAR)**

![Diagram showing Vincent scale for pain intensity with shaded areas representing patient pain and total pain relief over time.]

**Rescue Analgesic Use**

![Diagram showing VAS scale with shaded areas representing patient pain and rescue analgesic use over time.]

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Oxford Centre for Respiratory Medicine, TIME1 Trial

TIME1 PROTOCOL, version 3.3 20/02/2013
TOTPAR calculation in presence of rescue medication

For analysis purposes if rescue medication is administered, it is taken that pain intensity reverts to initial pain intensity over the next 4 hours.
APPENDIX 4 – SERIOUS ADVERSE EVENT FLOWCHART

Serious Adverse Event (SAE)
Not notifiable adverse event as specified in section 10

- Cease trial medication if taking until discussed with trial team
- Principal Investigator contacts Trial Team within 1 working day of awareness (telephone / fax form)
  Trial mobile number: 07969 614819
  RTU number: 01865 225205

? Possible SUSAR on basis of discussion

- No
  - Complete SAE form and send to Oxford Team
  - Clinical decision to continue trial drugs as discussed with trial team
  - Yes
    - Complete the course of trial medication and record details on appropriate forms.
  - No
    - Do not complete the course of trial medication and record details on appropriate forms.

- Yes (no further trial drugs to be given)
  - Expedited reporting to Sponsor / MHRA / Ethics
    (Within 7 working days if death/life threatening or within 15 if not)

- Co-ordinating Centre to Supervise
  - Immediate contact with MRC CTU