This supplement contains the following items:

1. Original protocol, final protocol, summary of changes.
2. Original statistical analysis plan.

There were no further changes to the original statistical analysis plan.
The Australasian Malignant Pleural Effusion Trial (AMPLE)

A Multicentre Randomized Study Comparing Indwelling Pleural Catheter vs Talc Pleurodesis in Patients with Malignant Pleural Effusions

Ethics Registration number 2012-005
Protocol version number 1.0
Protocol date 10/01/2012

Authorised by:

Name: Prof YC Gary Lee
Role: Chief Investigator

Signature: Date: 10/01/2012
General Information

This document describes the Western Australian Randomised Malignant Effusion trial for the purpose of submission for review by the relevant human research and ethics committees. It provides information about procedures for entering patients into the trial and this protocol should not be used as a guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Questions or problems relating to this study should be referred to the Chief Investigator or Trial Coordinator.

Compliance

The trial will be conducted in compliance with this protocol, the National Statement on Ethical Conduct in Human Research, data protection laws and other guidelines as appropriate. It will be registered with the Australia and New Zealand Clinical Trials Registry, once ethical approval is secured.

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ABBREVIATIONS

AE       Adverse Event
CRF      Case Report Form
TMF      Trial Master File
CTP      Clinical Study Protocol
CTR      Clinical Study Report
FDA      Food and Drugs Administration (USA)
GCP      Good Clinical Practice
HREC     Human Research Ethics Committee
ICH      International Conference on Harmonisation
IPC      Indwelling Pleural Catheter
IEC      Independent Ethics Committee
IRB      Institutional Review Board
SAE      Serious Adverse Events
SCGG     Sir Charles Gairdner Group
SOP      Standard Operating Procedure
1. Lay summary

A cancer induced collection of fluid between the lung and the chest wall (a malignant pleural effusion) affects ~15,000 new patients each year (Australia), including 25% of patients with lung cancer, 95% with mesothelioma and 40% with breast cancer. In WA alone the annual cost of inpatient care of this condition is currently $12 million, representing a major health burden for the state.

The accumulated fluid compresses the lung and weighs on the diaphragm, causing disabling breathlessness that requires painful pleural procedures to drain the fluid. The average life expectancy for patients with this condition is just 3 to 9 months, and therefore it is crucial to minimise hospital admissions and maximise time spent with loved ones.

A variety of management strategies exist for the management of malignant effusions, though there is no general consensus governing the best choice. Conventional care involves in-patient drainage of the effusion and performing talc pleurodesis – it can be painful and has a success rate of about 70% even in selected patients. Each procedure requires an average of 6 bed days and carries significant costs. Failure necessitates multiple further procedures and admissions to hospital. Ambulatory indwelling small-bore chest catheters, drained as required by patients and/or carers, present a new FDA-approved strategy that requires only outpatient management and is free from the side effects and costs of pleurodesis. Experience in North America and Europe suggest that uptake of this treatment and the magnitude of its cost savings depend on cultural factors and local health system costs.

This study is a randomised trial which will compare the total number of days in hospital for patients treated with indwelling catheter compared to talc pleurodesis in 146 patients with cancer induced pleural effusion. It will measure the frequency of problems with the two treatment strategies. If this trial is positive, it will directly improve care for one of the commonest respiratory problems, to the benefit of ~15,000 patients each year.

2. Abstract and summary of trial design

Malignant pleural effusion affects ~15,000 patients annually (Australia-wide). It causes breathlessness and requires painful pleural procedures. Standard care is inpatient pleurodesis, repeated if needed and followed by pleural aspirations if it fails. This is painful, occasionally causes life threatening adverse events, and carries substantial costs. Ambulatory indwelling pleural catheters drained by patients and their carers may be a better strategy. Treatment is mostly outpatient, with patient controlled fluid drainage avoiding inpatient pleurodesis; though with the disadvantage of the catheter. Our pilot data suggests this is
superior in reducing bed days. This protocol describes a randomised (trial entry) controlled trial to assess whether these benefits are genuine.

146 patients will be randomised 1:1 to an ambulatory catheter or standard care. This sample size was determined by power calculations derived from our pilot study entitled “Longitudinal Follow Up on Management of Malignant Pleural Effusions” (SCGG HREC no. 2009-104). The number of days in hospital will be recorded for the rest of the patients’ lives (1° endpoint). Self reported quality of life and breathlessness scores (using the same tools as used in the pilot study), adverse events and health care costs will be recorded. Comparison of the outcomes in the two groups will define whether ambulatory pleural catheters are superior to talc pleurodesis in keeping these patients out of hospital, improving their symptoms, and whether or not they are cost effective and safe. A positive result from this trial will improve treatment for ~15,000 respiratory patients each year.

2.1 Type of design

Randomised (trial entry) controlled trial to evaluate whether indwelling pleural catheter management of malignant effusion reduces bed days compared to talc pleurodesis (1° endpoint).

2.2 Disease and patients studied

Patients will be identified from outpatient clinics at Sir Charles Gairdner, Fremantle, Royal Perth, Princess Alexandra and Wellington Hospitals. Screening criteria are based on normal practice and consecutive eligible patients will be offered trial entry. The principal investigator or a nominated member of staff will approach participants who fulfil the criteria for inclusion in the trial. Screening logs will be kept.

Inclusion Criteria
1. Patients must have a symptomatic malignant pleural effusion requiring intervention. The diagnosis may be established by:
   a) histocytologically proven pleural malignancy or
   b) recurrent large exudative pleural effusion with histologically proven cancer outside the thorax and no alternative cause.
2. Written informed consent.

Exclusion Criteria
1. Age < 18 years
2. Effusion smaller than 2cm at maximum depth
3. Expected survival <3 months
4. Chylothorax
5. Previous lobectomy or pneumonectomy on the side of the effusion
6. Previous attempted pleurodesis
7. Pleural infection
8. Total blood white cell count <1.0 x 10^9/l
9. Hypercapnic ventilatory failure
10. Patients who are pregnant or lactating
11. Irreversible bleeding diathesis
12. Irreversible visual impairment
13. Inability to give informed consent or comply with the protocol

2.3 Trial treatments – intervention and control

Patients will be randomly assigned (1:1) to either an indwelling ambulatory pleural catheter or talc pleurodesis for their malignant pleural effusion.

Computer derived allocation will be delivered by an established, nationally recognised randomisation system at Wellington Hospital, NZ. There will be a block randomisation with a block size of six, stratified by study centre. Randomisation will include minimisation for histological tissue type (mesothelioma vs. non-mesothelioma) since survival is increased in mesothelioma, and the risk of catheter associated subcutaneous tumour invasion may be higher with mesothelioma; and the presence of trapped lung, since this has been postulated to reduce the likelihood of a successful pleurodesis. A statistician, not involved in the trial, will manage the allocation sequence.

2.4 Outcome measures

Primary endpoint:

The number of days spent in hospital (bed days) for any cause for all hospital admissions following intervention, until death or the end of the study follow-up. The primary endpoint is chosen as it is the most meaningful outcome for cancer patients and their clinicians. Hospital admissions will be further categorized and the days of admissions directly attributable to the pleural effusion and/or its treatment will be recorded as “effusion-related” (a secondary endpoint).

Given the impossibility of blinding, hospital admissions will be decided by the independent treating physicians, not by the investigators wherever possible. The reason(s) for admission must be documented and satisfy at least one of the following criteria:

- A procedure is required that cannot be performed in the outpatient setting because of the need for >2 hours of close nursing or medical attention.
• A coexisting or new medical problem requires inpatient therapy.
• Cancer or effusion-related symptoms cannot be adequately controlled at home with community nursing, GP and outpatient clinic support.

Incomplete days, eg day procedure admission for IPC-insertion, will be rounded up to 1 complete day. Day-case chemotherapy administration will not be included as admissions. The validity of all investigator-initiated admissions will be independently assessed by a preapproved assessor within one month of the event occurring.

**Secondary endpoints:**

• Admissions (days and number of episodes) for pleural effusion-associated causes. This includes admissions for management of pleural effusion, associated symptoms, related procedures and/or their complications.
• Survival and adverse events from enrolment to death or end of follow-up.
• Breathlessness (visual analogue) score recorded daily and self-reported quality of life scores at monthly intervals and for 1 day before and 1 week after any procedure.
• Health cost assessment: direct clinical costs from WA Health Dept coding data and other estimated community-based costs will be captured from patient diary records.

**2.5 Duration**

Patients will be followed up for a minimum of 6 months after recruitment (or until death) with outcome assessments at randomisation, 10-14 days, then fortnightly for 8 weeks, then monthly to 6 months and three monthly until the end of the study. Data will be recorded in duplicate on case report forms (CRFs).

**2.6 Trial Committees and Adverse Event Management**

**Trial Management Committee:**
- Prof YC Gary Lee (CI, SCGH)
- Dr E Fysh (Trial Coordinator)
- Prof G Waterer (AI, Royal Perth Hospital)
- Prof P Kendall (AI, Fremantle Hospital)

**Trial Steering Committee:**
- Prof S Spiro (Independent Chairman)
- Prof YC Gary Lee (CI)
- Dr N Rahman (Independent Expert)
- Dr E Fysh (Trial Coordinator)
The Trial Steering Committee 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 ethical standards, monitoring for adverse events and for determining the need for early cessation of the trial. As these are approved treatments there is no requirement for a Safety Committee.

3. ADMINISTRATIVE MATTERS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant BI SOPs. Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in the responsibility of the treating physician of the patient.

The study will be carried out in accordance with the harmonized standards for Medical Devices (ISO 14155-01 and ISO 14155-02) and all other applicable regulatory requirements.

3.1. ETHICS

3.1.1 Independent Ethics Committee or Institutional Review Board

The study will not be initiated before the clinical trial protocol (CTP) and informed consent and patient information form have been reviewed and received approval / favourable opinion from the local Institutional Review Board (IRB) / Independent Ethics Committee (IEC) and other regulatory authorities as required by local laws and regulations. Should a CTP amendment be made that needs IRB / IEC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IRB / IEC and other regulatory authorities as required by local laws and regulations. A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IRB / IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification only of the IRB / IEC and other regulatory authorities as required by local laws and regulations.

3.1.2 Patient Information and Informed Consent

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH GCP and to the regulatory and legal
requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors (CML/CRA) or Clinical Quality Assurance auditors appointed by appropriate IRB / IEC members, and by inspectors from regulatory authorities.

Should a CTP amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the CTP. It is the responsibility of the investigator to ensure that an amended consent form is reviewed and has received approval / favourable opinion from the IRB / EC and other regulatory authorities, as required by ICH GCP and by local laws and regulations, and that it is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

3.2 RECORDS

3.2.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to also investigate any inconsistencies using medical records. These medical records will be available to the investigator as one of the patient’s treating physicians.

3.2.2 Trial Master File (TMF)

A Trial Master File (TMF) will be created containing all the study documents including all ethics correspondence (emails and letters), and copies of the approved documentation for the study.
3.2.3 Unique Identification Code
Each study patient will have a unique study identification code created following informed consent which will comprise their first name and last name initials and a consecutive number generated at the time of randomisation. Study participants will have individual trial notes which will be kept in a secure location in the SCGH Respiratory Department, separate to the participant’s medical records.

4. PROCEDURES

4.1 ADVERSE EVENTS
An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition in a patient in a clinical investigation who received an experimental procedure. The event does not necessarily have to have a causal relationship with this treatment.

All adverse events occurring during the course of the clinical study (i.e., from signing the informed consent to the follow-up clinic visit post pleural procedure will be collected, documented and reported to the Ethics Department by the investigator according to the specific definitions and instructions detailed in the ‘Adverse Event Reporting’ section of the Trial Master File.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

All adverse events, serious and non-serious, will be fully documented on the appropriate CRFs. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken. The investigator will determine the relationship of the experimental procedure to all AEs as defined in the ‘Adverse Event Reporting’ Section of the Investigator Site File.

The basis for judging the intensity of the AE as well as the causal relationship between the experimental procedure and the AE is described below.

Intensity of event
• Mild: Awareness of sign(s) or symptom(s) which is/are easily tolerated
• Moderate: Enough discomfort to cause interference with usual activity
• Severe: Incapacitating or causing inability to work or to perform usual activities

Causal relationship
Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.
• Yes: There is a reasonable causal relationship between the experimental procedure and the AE.
• No: There is no reasonable causal relationship between the experimental procedure and the AE.

If a SAE is reported, the causal relationship must be provided by the investigator. The investigator has the obligation to report AEs during the specified time of the study. If defined in the CTP, the investigator also has the responsibility to report AEs occurring in a certain period after a patient completes the study. If not stipulated differently in the TMF, SAEs are to be reported to the ethics committee using the Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

Any serious or significant AE, whether or not considered related to the experimental procedure must be reported as soon as it becomes apparent to the Ethics Department using the reporting procedure and associated documentation according to local regulatory requirements.

7. Data Quality Assurance

The study will be conducted according to the principles of Good Clinical Practice (GCP) and local standard operating procedures (SOPs). The accuracy of the data will be verified by comparing study data to source documents. Medical records and progress notes will be kept accurate and up to date and available at all times for inspection in the event of audit.

6. Publication Policy

As a general rule, no study results should be published prior to finalisation of the Clinical Study Report (CTR).
7. **Completion of Study**

The Sir Charles Gairdner Group HREC will be notified about the end of the study (last patient/patient out) or if the study is terminated early.

8. **Data Handling and Record Keeping**

All procedures for the handling and analysis of data will be conducted using GCP meeting ICH guidelines and the Australian Human Research Ethics Committees, or local equivalent for the handling and analysis of data for clinical trials.

8.1 **Data Quality Control and Reporting**

After data have been entered into the study database, a system of data validation checks will be implemented and applied to the database. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.

8.2 **Records Retention**

The study site will retain all records related to the study in accordance with local and ICH GCP guidelines in order to comply with applicable regulatory requirements.

9. **References**


10. FLOWCHART

Figure 1: Trial entry, randomisation, trial treatment and follow up care.

### Trial Entry
1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis may be established by:
   a) Histocytologically proven pleural malignancy
   or
   b) Recurrent large pleural effusion in the context of histologically proven cancer outside the thorax.
2. Written informed consent

### RANDOMISE

### Ambulatory indwelling pleural catheter drainage
- Day-case catheter insertion
- Attendance day 10 to 14 for drainage, stitch removal and education in catheter care

### Talc Pleurodesis
- Admission to hospital
- 12F chest drain insertion
- Pleural suction if indicated
- Talc pleurodesis (if >75% of visceral and parietal pleura in direct contact on CXR)

### Follow up
At 10-14 days, then fortnightly for 8 weeks, then monthly to 6 months and three monthly to 12 months
= Out-patients assessment (data collection, health questionnaires, spirometry)
11. APPENDIX

11.1 Patient Information Sheet

Randomised Clinical Trial of Indwelling Pleural Catheter or Pleurodesis for Patients with Malignant Pleural Effusion. Trial No. 2012-005

Researchers
Professors YC Gary Lee, Bill Musk, Michael Millward, Grant Waterer, Peter Kendall, Dr Edward Fysh and Sister Sue Morey

*Please take time to read the following information carefully and discuss it with your friends, family and general practitioner if you wish. Ask us any question if some part of the information is not clear to you or if you would like more information. Please do this before you sign this consent form.*

Who is funding this study?
This study has been funded by the Sir Charles Gairdner Research Advisory Committee, and Dr Fysh receives a scholarship from the National Health and Medical Research Committee. The indwelling pleural catheters are provided by Rocket Medical PLC.

CONTACT PERSONS:

**Should you have questions about the study you may contact:**
Dr Edward Fysh: Phone No. 9346 3333/ 0421253918
Professor Y C Gary Lee: Phone No. 9346 4968

All study participants will be provided with a copy of the Information Sheet for their personal records.

You may decide to be in the study or not take part at all. If you do decide to take part in this study, you may stop at any time. However, before you decide, it is important that you understand why this research is being done and what it will involve.

Whatever your decision, this decision will not lead to any penalty or affect your regular medical care or any benefit to which you are otherwise entitled.

*The following information sheet will explain the study and will include details such as:*
  - Why this trial might be suitable for you;
  - The possible risks (side-effects) and benefits of the new procedure;
  - The type, frequency and risks of any medical tests or procedures required by the trial;
The nature of your participation including how many visits you will make to the hospital;
Your rights and responsibilities;
Alternative treatments available to you.

What is the purpose of the study?
This multicentre randomized clinical trial aims to compare the potential benefits of employing indwelling small-bore pleural catheters (IPCs) as first-line management of malignant pleural effusion as opposed to pleurodesis, especially in reducing the need for inpatient hospital care for these patients. The study also evaluates the symptoms and quality of life, adverse event rates, and health costs associated with the 2 management options. Patients will be randomized to either IPC or pleurodesis, both approved hospital treatments.

We would also like to collect any of the drained fluid (which would otherwise be discarded) for research purposes. If your doctor requests a blood test for a clinical reason, we would ask to collect an extra small amount (10-20 millilitres) for research into the cause of these effusions. These samples would be stored in our secure research facilities at Sir Charles Gairdner Hospital for up to 5 years. They would be tested for markers of inflammation, infection and cancer.

Background Information:
Patients with cancer often develop a collection of fluid outside their lungs but within their chest cavity (a pleural effusion). In some patients, these fluid collections can lead to symptoms such as breathlessness on exertion, coughing, or pain.

When symptoms arise, there are several treatment options. One option is sticking a needle between the ribs to drain the fluid – this only provides temporary relief, and usually the fluid will recur. The more definitive treatment options are Pleurodesis or tunneled Indwelling Pleural Catheter (IPC).

Pleurodesis means inducing scarring of the surface of the lung to seal the pleural space to stop fluid from accumulating. This can be performed by surgery under sedation or general anaesthesia, or the patient can be admitted to hospital during and a tube can be placed between the ribs and a compound (usually talc powder) is inserted to induce pleurodesis. Pleurodesis has a success rate of about 75% in suitable patients. It can cause pain and fever and occasionally worsen the breathlessness.

Indwelling pleural catheters (IPC) are an approved treatment involving a day procedure to insert a small tube between the ribs which can be left buried underneath the skin of the chest with a small ending above the skin. The patient is usually able to return home the same day, and when the fluid builds up again the catheter enables them to drain the fluid at home or in the outpatient clinic without needing admission to hospital. There is a small risk (3%) of infection if the catheter is left for several months.

Whilst both treatments are safe, effective and widely used, there is no evidence yet that shows conclusively which treatment is the better option in the various different patient circumstances. This is why a study directly comparing these therapies is required.

Why is this study suitable to me?
You have been chosen to consider taking part in this trial because you have symptoms from the fluid which has accumulated around your lung due to your cancer. In the past the standard treatment involved an inpatient stay in hospital and attempted pleurodesis. In the last decade indwelling catheters (IPC) have become available. We are trying to find out if the insertion of an IPC is a better strategy. Since your fluid needs treatment to control it, we are asking you if you would consider taking part in this study to define if indwelling catheters are superior in terms of relief from your breathlessness and keeping you out of hospital, as compared to pleurodesis.

How long will I be in this study?

AMPLE protocol Version 1  10/01/2012
We will follow you up through the course of your illness to see if the treatment options are successful.

**What will happen if I decide to be in this study?**

One of the study investigators will talk to you, take a medical history from you and assess your suitability for the study. They will then give you this information sheet to read, and you will be given time to consider this, ask questions, and discuss it with your family and friends. If you decide to take part you will be given a consent form to sign. Once you have given your consent your treatment will be allocated by a randomisation process. Each participant is put into a group by chance (random) like tossing a coin. You and your doctor will not be able to choose which treatment you get. You will have a 50:50 chance of undergoing talc pleurodesis or IPC. We will undertake the assigned treatment as soon as possible to ensure quick relief of your symptoms. We may collect the evacuated fluid (which would otherwise be discarded) for future research on what causes the fluid to develop. It will be tested for inflammatory markers, infection, and possibly for cancer cells. With your optional consent, when you have any blood tests for other reasons we will also collect an extra 5-10 ml of blood for the same future research.

Follow up will be conducted at the respiratory outpatient clinic at Sir Charles Gairdner Hospital. Your first follow up appointment will be 10-14 days after your procedure. At these visits you will be asked some questions about your breathing, quality of life, and any problems you have encountered since we last reviewed you. You may have a chest x-ray and/or an ultrasound scan. If you have an IPC you may have some fluid drained to relieve shortness of breath.

The standard schedule for follow up will then be fortnightly for visits 2-4, and then 4 weeks apart for visits 5-8. After that your visits will be every 3 months. However, if you develop symptoms at any point, call Dr Fysh on the above mobile number and we will arrange extra appointments and appropriate treatment as soon as possible. If you find that you need to change your study appointment date or time please let us know as soon as possible.

**Are there any reasons I should not be in this study?**

Study staff will discuss these with you in detail and will ensure that this trial is both safe and appropriate for you. We would emphasize that participation in the study is entirely voluntary.

**What are the costs to me?**

You will incur no costs for participating in this study.

**What are the possible benefits of taking part, to me and to the wider community?**

The study is primarily aimed at assessing the outcome of these 2 different management options for malignant pleural effusions, so there will be no direct benefit to you by participating. You will have direct access by mobile phone to a study doctor in the event of symptoms recurring, and therefore will not have to wait for an appointment, or present to an emergency department before having these symptoms addressed.

**How will my safety be ensured?**

As this study does not involve any additional or alternative procedures that are not already fully approved and accepted treatments, there is no additional hazard for you in joining this study.

**What are my alternatives if I do not want to participate in this study?**

The alternative is that you do not have to participate in this study. You will still receive the appropriate medical care from your doctor, including one of the above approved treatment options as required.
What are the possible side effects, risks and discomforts of taking part?
What we ask of you in this study is to allow us to follow your progress (through outpatient visits, hospital record searches and maybe occasional telephone follow up) to see whether your treatment was successful and if you are satisfied. There is no additional risk to your health from participating in the study.

What if new information comes along during the study?
Sometimes during the course of a study, new information becomes available about the procedures that are being studied. While you are participating in this study, you will be told of any significant new findings which may affect your willingness to continue in the study.

Could the study be stopped early?
Sometimes a study may need to be stopped. Reasons a study may end early include: safety concerns for the participants; because other treatments or more effective treatments become available; because the researcher chooses to stop the study early, or for other reasons. If this does occur, you will be notified of the reasons, if known, and other treatment/care will be offered for your condition.

What happens at the end of the study?
At the end of the study you will continue under the care of your usual doctors.

What if something goes wrong?
Each of the treatment options for malignant pleural effusions has pros and cons and carries potential side effects. Your doctor will discuss your symptoms and treatments with you and if your initial treatment option fails you will be offered alternative treatments.

Participation in this study does not include unapproved or poorly understood treatments. Both treatment options are standard treatments available to any patient with your condition. This study merely allows us to follow your progress and record your treatment outcome, comparing the 2 alternatives. Therefore your participation will not bring additional risks.

Your participation in this study does not prejudice any right to compensation which you may have under statute or common law.

You will receive the best medical care available during and after this study. In the unlikely event that you experience any research-related harm as a result of taking part in this study, you will be provided with medical treatment/care at no cost to you. The term “research-related harm” means both physical and mental injury caused by the study procedures required by the trial.

Will my taking part in this study be kept confidential?
The researchers will need to collect personal data about you, e.g. date of birth and relevant health information. The researchers may also need to get some of your health information form other health service providers, eg another hospital, pathology laboratory, radiography (please note that your that CT/MRI scans may be reviewed), GP or other medical specialist.

Any personal or health information will be kept private and confidential. It will be stored securely and only authorised persons, who are aware that it must be kept confidential, will have access to it. Your study details will be given a number so your identity will not be revealed. The trial records will be kept in the Department of Respiratory Medicine during the study and in a locked archive for at least 5 years from the time the study is closed. They may be destroyed at any time thereafter.

Authorised representatives of the investigating doctor, the Hospital Human Research Ethics Committee, Research Governance and therapeutic regulatory bodies may require access to your
study records to verify study procedures and/or data. Some of your information may be sent to people in other countries for these purposes. In all cases when dealing with your information, these people are required to comply with privacy laws that protect you.

The result of the research will be made available to other doctors through medical journals or meetings, but you will not be identifiable in these communications. By taking part in this study you agree not to restrict the use of any data even if you withdraw. Your rights under any applicable data protection laws are not affected.

**How can I find out the results of the study?**
We intend to publish the results of the study in medical journals and present them to colleagues at medical meetings and conferences so that we can learn from the results of this study.

**Who has reviewed the study?**
The Sir Charles Gairdner Group Hospital Human Research Ethics Committee has reviewed this study and has given its approval for the conduct of this research trial. In doing so, this study conforms to the principles set out by the National Statement on Ethical Conduct in Research involving Humans and according to the Good Clinical Practice Guidelines.

**In the case of a medical emergency you should call:**
The Sir Charles Gairdner Hospital Pleural Disease Service –
Mobile: 0421253918
Via Switchboard: 93463333
11.2 Consent form

Consent Form
HREC Trial No. 2012-005

A Multicentre Randomized Study Comparing Indwelling Pleural Catheter vs Talc Pleurodesis in Patients with Malignant Pleural Effusions

Subject Name: __________________________ Date of Birth: _______________

1. I have been given clear information (verbal and written) about this study and have been given time to consider whether I want to take part.

2. I have been told about the possible advantages and risks of taking part in the study and I understand what I am being asked to do.

3. I have been able to have a member of my family or a friend with me while I was told about the study if I so wish. I have been able to ask questions and all questions have been answered satisfactorily.

4. I know that I do not have to take part in the study and that I can withdraw at any time during the study without affecting my future medical care. My participation in the study does not affect any right to compensation, which I may have under statute or common law.

5. I agree to take part in this research study and for the data obtained to be published provided my name or other identifying information is not used.

6. Tick appropriate boxes:
   - I agree to my blood samples being used in this trial  
   - I also agree to blood being stored for up to 10 yrs and being used in future ethically approved research projects.  
   - I agree to my pleural fluid being used in this trial  
   - I also agree to pleural fluid being stored for up to 10 yrs and being used in future ethically approved research projects.

If you are unclear about anything you have read in the Patient Information Sheet or this Consent Form, please speak to your doctor before signing this Consent Form.

Name of Patient    Signature of Patient    Date

Name of Investigator    Signature of Investigator    Date

The Sir Charles Gairdner Group Human Research Ethics Committee has given ethics approval for the conduct of this project. If you have any ethical concerns regarding the study you can contact the secretary of the Sir Charles Gairdner Group Human Research Ethics Committee on telephone No. (08) 9346 2999.
### 11.3 Symptom and Quality of Life Questionnaires

**Date:** __/__/__  
**Patient’s trial ID:**

By marking a score anywhere between 0 and 10 in the box provided, please indicate how you feel in each of the categories below. 10 is the best imaginable, and 0 the worst.

**Mobility:**  
10 = no problems walking about  
0 = confined to bed

**Self-Care:**  
10 = I have no problems with self-care  
0 = I am unable to wash and dress myself

**Usual Activities:** (e.g. work, housework, leisure activities)  
10 = I am unlimited in my usual activities  
0 = I am unable to undergo any of my usual activities

**Discomfort/Pain:**  
10 = No discomfort at all  
0 = The worst pain imaginable

**Anxiety/Depression**  
10 = I am not at all anxious or depressed  
0 = I am extremely anxious or depressed
To enable you to best describe how good or bad your shortness of breath and your quality of life is on a given day we have drawn a scale on which the best state you can imagine is marked 100, and the worst you can imagine is marked 0.

Please mark your shortness of breath score with an “S” and quality of life with a “Q” the day before (1), the day after (2), and every subsequent day for a week (3-8) after any procedure to drain your fluid. If you need more space please contact us. Once complete, please return this sheet in the envelope provided.
The Australasian Malignant Pleural Effusion Trial (AMPLE)

A Multicentre Randomized Study Comparing Indwelling Pleural Catheter vs Talc Pleurodesis in Patients with Malignant Pleural Effusions

Ethics Registration number 2012-005 (SCGG)
Protocol version number 4.0
Protocol date 05/05/2014

Authorised by:

Name: Prof YC Gary Lee
Role: Chief Investigator

Signature: 
Date: 05/05/2014
**General Information**

This document describes the Australasian Malignant Pleural Effusion trial for the purpose of submission for review by the relevant human research and ethics committees. It provides information about procedures for entering patients into the trial and this protocol should not be used as a guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. Questions or problems relating to this study should be referred to the Chief Investigator or Trial Coordinator.

**Compliance**

The trial will be conducted in compliance with this protocol, the National Statement on Ethical Conduct in Human Research, data protection laws and other guidelines as appropriate. It will be registered with the Australia and New Zealand Clinical Trials Registry, once ethical approval is secured.

**Main Contacts:**

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ABBREVIATIONS

AE    Adverse Event
CRF   Case Report Form
CTR   Clinical Study Report
DSMC  Data Safety Management Committee
EC    Ethics Committee
FDA   Food and Drugs Administration (USA)
GCP   Good Clinical Practice
HREC  Human Research Ethics Committee
ICH   International Conference on Harmonisation
IPC   Indwelling Pleural Catheter
MPE   Malignant Pleural Effusion
SAE   Serious Adverse Events
SCGG  Sir Charles Gairdner Group
SCGH  Sir Charles Gairdner Hospital
SOP   Standard Operating Procedure
TMF   Trial Master File
TSC   Trial Steering Committee
1. LAY SUMMARY

A cancer induced collection of fluid between the lung and the chest wall (a malignant pleural effusion) affects ~15,000 new patients each year (Australia), including 25% of patients with lung cancer, 95% with mesothelioma and 40% with breast cancer. In WA alone the annual cost of inpatient care of this condition is currently $12 million, representing a major health burden for the state.

The accumulated fluid compresses the lung and weighs on the diaphragm, causing disabling breathlessness that requires painful pleural procedures to drain the fluid. The average life expectancy for patients with this condition is just 3 to 9 months, and therefore it is crucial to minimise hospital admissions and maximise time spent with loved ones.

A variety of management strategies exist for the management of malignant effusions, though there is no general consensus governing the best choice. Conventional care involves in-patient drainage of the effusion and performing talc pleurodesis – it can be painful and has a success rate of about 70% even in selected patients. Each procedure requires an average of 6 bed days and carries significant costs. Failure necessitates multiple further procedures and admissions to hospital. Ambulatory indwelling small-bore chest catheters, drained as required by patients and/or carers, present a new FDA-approved strategy that requires predominantly outpatient management and is free from the side effects and costs of pleurodesis. Experience in North America and Europe suggests that uptake of this treatment and the magnitude of its cost savings depend on cultural factors and local health system costs.

This study is a randomised trial which will compare the total number of days in hospital for patients treated with indwelling catheter compared to talc pleurodesis in 146 patients with cancer-induced pleural effusion. It will measure the frequency of problems with the two treatment strategies. If this trial is positive, it will directly improve care for one of the commonest respiratory problems, to the benefit of ~15,000 patients each year.

2. ABSTRACT AND SUMMARY OF TRIAL DESIGN

Malignant pleural effusion affects ~15,000 patients annually (Australia-wide). It causes breathlessness and requires painful pleural procedures. Standard care is inpatient pleurodesis, repeated if needed and followed by pleural aspirations if it fails. This is painful, occasionally causes life threatening adverse events, and carries substantial costs. Ambulatory indwelling pleural catheters drained by patients and their carers may be a better strategy. Treatment is mostly outpatient, with patient controlled fluid drainage avoiding inpatient pleurodesis;
though with the disadvantage of the catheter. Our pilot data suggests this is superior in reducing bed days. This protocol describes a randomised (trial entry) controlled trial to assess whether these benefits are genuine.

146 patients will be randomised 1:1 to an ambulatory catheter or standard care. This sample size was determined by power calculations derived from our pilot study entitled “Longitudinal Follow Up on Management of Malignant Pleural Effusions” (SCGG HREC no. 2009-104). The number of days in hospital will be recorded for the rest of the patients’ lives (1° endpoint). Self reported quality of life and breathlessness scores (using the same tools as used in the pilot study), adverse events and health care costs will be recorded. Comparison of the outcomes in the two groups will define whether ambulatory pleural catheters are superior to talc pleurodesis in keeping these patients out of hospital, improving their symptoms, and whether or not they are cost effective and safe. A positive result from this trial will improve treatment for ~15,000 respiratory patients each year.

2.1 Type of design
Randomised (trial entry) controlled trial to evaluate whether indwelling pleural catheter management of malignant effusion reduces bed days compared to talc pleurodesis (1° endpoint).

2.2 Disease and patients studied
Patients will be identified from outpatient clinics. Screening criteria are based on normal practice and consecutive eligible patients will be offered trial entry. The principal investigator or a nominated member of staff will approach participants who fulfil the criteria for inclusion in the trial. Screening logs will be kept.

2.2.1 Inclusion Criteria
1. Patients must have a symptomatic malignant pleural effusion requiring intervention. The diagnosis may be established by:
   a) histocytologically proven pleural malignancy

   or

   b) recurrent large exudative pleural effusion with histologically proven cancer outside the thorax and no alternative cause.

2. Written informed consent.

2.2.2 Exclusion Criteria
1. Age < 18 years
2. Effusion smaller than 2cm at maximum depth
3. Expected survival <3 months
4. Chylothorax
5. Previous lobectomy or pneumonectomy on the side of the effusion
6. Previous attempted pleurodesis
7. Pleural infection
8. Total blood white cell count < 1.0 x 10^9/l
9. Hypercapnic ventilatory failure
10. Patients who are pregnant or lactating
11. Irreversible bleeding diathesis
12. Irreversible visual impairment
13. Inability to give informed consent or comply with the protocol

2.3 Trial treatments – intervention and control

This study randomizes patients to receive one of two treatments for malignant pleural effusions: talc pleurodesis and indwelling pleural catheter (IPC) placement. Both options are approved and established therapies for recurrent (including malignant) effusions. The delivery of each of the therapy and its aftercare will be provided by each centre according to its usual practice protocols, and are not specified in this trial. Minor variations in the protocols are expected as there is no agreed or proven best practice in the detailed techniques of these procedures.

The local PI will be responsible for ensuring that only properly doctors trained carry out, or supervise, the procedure.

2.3.1 Bedside Talc pleurodesis procedure

Bedside talc pleurodesis is a commonly used treatment to induce pleural symphysis and obliterate the pleural space to prevent accumulation of pleural effusions. Talc is delivered as a slurry via a chest tube which will be clamped for a short (usually 1 to 4 hours) time. Each centre will perform the talc pleurodesis as per their usual practice which includes the size of chest drain used, timing of talc instillation and chest drain removal etc.

2.3.2 IPC Management

IPC has been FDA approved since the initial safety trials in the late 1990s. The catheter remains in situ as long as it is needed, but can be removed if fluid production stops, or otherwise clinically indicated. All patients are given an information sheet (which they can also show to the community nurses) with detailed instructions and contact details for support. Patients with IPCs have the support and care of the experienced community respiratory nurse, as per standard care. The attending clinician will decide on the details of aftercare as most suitable for individual patients. This will include drainage frequencies, personnel performing the drainage etc as well as managed for any complications that may or may not arise.
2.4 Randomisation

Patients will be randomly assigned (1:1) to either an indwelling ambulatory pleural catheter or talc pleurodesis for their malignant pleural effusion.

Randomisation will include minimisation for i) Australasian centres vs centres outside Australasia; ii) histological tissue type (mesothelioma vs. non-mesothelioma) since survival is increased in mesothelioma, and the risk of catheter associated subcutaneous tumour invasion may be higher with mesothelioma; and iii) the presence of trapped lung, since this has been postulated to reduce the likelihood of a successful pleurodesis. An independent specialist with expertise in trial statistics and randomization setup, who is not involved in the study, will manage the allocation sequence.

To maintain allocation concealment, randomisation is performed in real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara). Initially, a minimisation program was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5-0.7 favouring the treatment that would minimise differences between groups on two key prognostic factors (mesothelioma and trapped lung). When Singapore was added as a site in late 2013, stratification by region (Australasia versus Singapore) was added to account for any potential differences in baseline characteristics between patient and disease cohorts. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable (1).


2.5 Outcome Measures

2.5.1 Primary Endpoint:
The number of days spent in hospital (bed days) for any cause for all hospital admissions following intervention, until death or the end of the study follow-up. The primary endpoint is chosen as it is the most meaningful outcome for cancer patients and their clinicians. Hospital admissions will be further categorized and the days of admissions directly attributable to the pleural effusion and/or its treatment will be recorded as “effusion-related” (a secondary endpoint).

Given the impossibility of blinding, hospital admissions will be decided by the independent treating physicians, not by the investigators wherever
possible. The reason(s) for admission must be documented and satisfy at least one of the following criteria:

- A procedure is required that cannot be performed in the outpatient setting because of the need for >2 hours of close nursing or medical attention.
- A coexisting or new medical problem requires inpatient therapy.
- Cancer or effusion-related symptoms cannot be adequately controlled at home with community nursing, GP and outpatient clinic support.

Incomplete days, eg day procedure admission for IPC-insertion, will be rounded up to 1 complete day. Day-case chemotherapy administration will not be included as admissions. The validity of all investigator-initiated admissions will be independently assessed by a preapproved assessor within one month of the event occurring.

### 2.5.2 Secondary Endpoints:

- Admissions (days and number of episodes) for pleural effusion-associated causes. This includes admissions for management of pleural effusion, associated symptoms, related procedures and/or their complications.
- Survival and adverse events from enrolment to death or end of follow-up.
- Breathlessness (visual analogue) score recorded daily and self-reported quality of life scores at monthly intervals and for 1 day before and 1 week after any procedure.
- Health cost assessment: direct clinical costs from local department coding data and other estimated community-based costs will be captured from patient data.
- Quality of Life data

### 2.6 Duration

Patients will be followed up for a minimum of 6 months after recruitment (or until death) with outcome assessments at randomisation, 10-14 days, then fortnightly for 8 weeks, then monthly to 6 months and three monthly until the end of the study. Data will be recorded in duplicate on case report forms (CRFs).
2.7 Trial Committees

**Trial Steering Committee (TSC):**

- Prof S Spiro (Independent Chairman)
- Prof YC Gary Lee (CI)
- Dr N Rahman (Independent Expert)
- Dr E Fysh (Trial Coordinator)
- Dr Rajesh Thomas (Trial Coordinator)

The Trial Steering Committee 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 ethical standards. It will review recommendations from the DSMC through their monitoring of adverse events and therefore determine whether there is a need for early trial cessation.

**Data Safety Monitoring Committee (DSMC):**

- Prof S Spiro (Independent Chairman)
- Dr N Rahman (Independent Expert)
- Ly-Mee Yu (Independent Statistician)

The Data and Safety Monitoring Committee (DSMC) will be charged with ensuring the safety of study participants through the monitoring of trial procedure adverse events, serious adverse events and considering new data (recently published studies). All deaths; anticipated and unanticipated will also be discussed with the DSMC.

Thus it determines whether significant benefits or risks have been uncovered which may have an impact on the feasibility and/or ethical conduct of the study.

The DSMC will also help to ensure the scientific integrity of the study by reviewing the quality of the data it uses to make its decisions.

The DSMC provides recommendations to the Trial Steering Committee (TSC), who oversees the study and determines whether the study should continue, be suspended or terminated. The ultimate decision about the study’s continuation does not rest with the DSMC.

3. Recruitment Process

Potential participants will be recruited from the respiratory medicine clinic. Outside respiratory medicine patients with a known or likely malignant pleural effusion which requires management to control symptoms will be identified by respiratory / haematology / medical oncology / radiation oncology teams. The potential patient will be approached about the possibility of taking part in the study if they are at the point of requiring intervention for the management of
their malignant pleural effusion. They will be given an explanation of the study by the doctor and then given the participant information and consent form (PICF) to read through and ask questions of the doctor. The patient can either provide informed consent whilst at clinic or can be given the option to take the PICF home to discuss further with family and their GP. They can then discuss further with the doctor when they return for their next clinic appointment. As both treatment options are well established and approved therapies one would be employed irrespective of whether the patient decided to be enrolled in the study.

4. STATISTICAL PLAN – MISSING DATA

In common with many clinical studies, missing data may exist either in form of total non-response (e.g. attrition due to death or patient withdrawal) or item non-response (when some but not all the required information is collected from the patients). We will attempt to minimize the missing data due to item non-response. Throughout the duration of the trial, participants will have regular contact with the respiratory department, as well as the research team. The patient will be asked to complete the forms whilst at clinic. This will maximise proper and complete data collection. The research team will document as accurately as possible the reasons for any non-completion or missing data, thereby minimising truly absent data. The expected dropout from patient death has been factored into the power calculation and is based on survival figures. The detail of the statistical analysis will be set out in the Statistical Analysis Plan.

5. SAMPLE SIZE CALCULATIONS

Sample size requirements - In order to examine the potential benefit of reduction in hospital stay using IPC, 62 patients in each group are needed to be able (with 80% power) to detect a difference between groups of 0.54 standard deviations (at the 2-sided 5% level) in any of the continuous variables. This is equivalent to an improvement of about 5 or more days in time spent in hospital, based on preliminary estimates of 18 days for post pleurodesis patients. To allow for a 20% lost-to-follow-up rate, an additional 24 patients will be needed, to make a total recruitment target of 146. This is likely an overestimate as no patient was lost to follow-up in the WAMPE (pilot) study (SCGG HREC no. 2009-104).

6. ADMINISTRATIVE MATTERS

The study will be carried out in compliance with the protocol, the principles laid down in the Declaration of Helsinki, version as of October 1996 (as long as local laws do not require to follow other versions), in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP) and relevant
6.1. Ethics

6.1.1 Ethics Committee

The study will not be initiated before the clinical trial protocol and informed consent and patient information form have been reviewed and received approval / favourable opinion from the Ethics Committee and other regulatory authorities as required by local laws and regulations. Should a protocol amendment be made that needs EC approval and authority notification/approval, the changes in the CTP will not be instituted until the amendment and revised informed consent (if appropriate) have been reviewed and received approval / favourable opinion from the local IEC and other regulatory authorities as required by local laws and regulations. A CTP amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing that the regulatory authority and IEC are notified as soon as possible and an approval is requested. CTP amendments exclusively for logistical or administrative changes may be implemented with notification only of the IEC and other regulatory authorities as required by local laws and regulations.

6.1.2 Participant Information and Informed Consent

Prior to patient participation in the study, written informed consent must be obtained from each patient (or the patient’s legally accepted representative) according to ICH GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient information form retained by the investigator as part of the study records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient’s legally accepted representative.

The patient must be informed that his/her personal study-related data will be used by the Principal Investigator in accordance with the local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his / her medical records may be examined by authorised monitors or Clinical Auditors appointed by appropriate EC members, and by inspectors from regulatory authorities.

Should a protocol amendment become necessary, the patient consent form and patient information form may need to be revised to reflect the changes to the protocol. It is the responsibility of the investigator to ensure that an
amended consent form is reviewed and has received approval / favourable opinion from the EC and other regulatory authorities, as required by ICH GCP and by local laws and regulations, and that it is signed by all patients subsequently entered in the study and those currently in the study, if affected by the amendment.

6.2 Records

6.2.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator’s site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to also investigate any inconsistencies using medical records. These medical records will be available to the investigator as one of the patient’s treating physicians.

6.2.2 Trial Master File (TMF)

A Trial Master File (TMF) will be created containing all the study documents including all ethics correspondence (emails and letters), and copies of the approved documentation for the study.

6.2.3 Unique Identification Code

Each study patient will have a unique study identification code created following informed consent which will comprise their first name and last name initials and a consecutive number generated at the time of randomisation. Study participants will have individual trial notes which will be kept in a secure location in the local Respiratory Department, separate to the participant’s medical records.

7. ADVERSE EVENTS

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition in a patient in a clinical investigation who received an experimental procedure. The event does not necessarily have to have a causal relationship with this treatment.

All adverse events relating to the trial procedure occurring during the course of the clinical study (i.e., from signing the informed consent until death or the end of the study follow up period (whichever comes first) will be collected and documented by the investigator according to the specific definitions and
instructions detailed in the ‘Adverse Event Reporting’ section of the Trial Master File. Cases will also be reported if a causal link between the AE and the trial procedure is suspected but not confirmed.

A serious adverse event (SAE) is defined as any AE which results in death, is immediately life-threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation, is a congenital anomaly / birth defect, or is to be deemed serious for any other reason if it is an important medical event when based upon appropriate medical judgment which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. In the context of this trial where the participants are people diagnosed with a life-limiting malignancy, anticipated deaths will not be reported as SAEs but reported in annual and final reports and discussed with the DSMB. Deaths that are not anticipated will be reported as SAEs in the usual manner.

All adverse events relating to the trial procedure, serious and non-serious, will be fully documented on the appropriate CRFs. For each adverse event, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken. The investigator will determine the relationship of the experimental procedure to all AEs as defined in the ‘Adverse Event Reporting’ Section of the Investigator Site File.

The basis for judging the intensity of the AE as well as the causal relationship between the experimental procedure and the AE is described below.

**Intensity of event**

- **Mild**: Awareness of sign(s) or symptom(s) which is/are easily tolerated
- **Moderate**: Enough discomfort to cause interference with usual activity
- **Severe**: Incapacitating or causing inability to work or to perform usual activities

**Causal relationship**

Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history. Assessment of causal relationship should be recorded in the case report forms.

- **Yes**: There is a reasonable causal relationship between the experimental procedure and the AE.
- **No**: There is no reasonable causal relationship between the experimental procedure and the AE.

If a SAE is reported, the causal relationship must be provided by the investigator. The investigator has the obligation to report AEs during the specified time of the study. If defined in the CTP, the investigator also has the

AMPLE protocol Version 4  05/05/2014  Page 16 of 22
responsibility to report AEs occurring in a certain period after a patient completes the study. If not stipulated differently in the TMF, SAEs are to be reported to the ethics committee using the Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible. With receipt of follow-up information, all remaining fields on the SAE form are to be completed or updated.

Any serious or significant AE, whether or not considered related to the experimental procedure must be reported as soon as it becomes apparent to the Ethics Department using the reporting procedure and associated documentation according to local regulatory requirements.

8. DATA QUALITY ASSURANCE

The study will be conducted according to the principles of Good Clinical Practice (GCP) and local standard operating procedures (SOPs). The accuracy of the data will be verified by comparing study data to source documents. Medical records and progress notes will be kept accurate and up to date and available at all times for inspection in the event of audit.

9. PUBLICATION POLICY

As a general rule, no study results should be published prior to finalisation of the Clinical Study Report (CTR).

10. COMPLETION OF STUDY

The Sir Charles Gairdner Group HREC will be notified about the end of the study (last patient/patient out) or if the study is terminated early.

11. DATA HANDLING AND RECORD KEEPING

All procedures for the handling and analysis of data will be conducted using GCP meeting ICH guidelines and the Australian Human Research Ethics Committees, or local equivalent for the handling and analysis of data for clinical trials.

11.1 Data Quality Control and Reporting

After data have been entered into the study database, a system of data validation checks will be implemented and applied to the database. The study database will be updated in accordance with the resolved query reports. All changes to the study database will be documented.
11.2 Records Retention

The study site will retain all records related to the study in accordance with local and ICH GCP guidelines in order to comply with applicable regulatory requirements.
12. REFERENCES


13. FLOWCHART

Figure 1: Trial entry, randomisation, trial treatment and follow up care.

**Trial Entry**
1. Clinically confident diagnosis of malignant pleural effusion requiring pleurodesis. The diagnosis may be established by:
   a) Histocytologically proven pleural malignancy or
   b) Recurrent large pleural effusion in the context of histologically proven cancer outside the thorax.
2. Written informed consent

---

**RANDOMISE**

---

**Ambulatory indwelling pleural catheter drainage**
Day-case catheter insertion
Attendance day 10 to 14 for drainage, stitch removal and education in catheter care

**Talc Pleurodesis**
Admission to hospital
12F – 18F chest drain insertion
Pleural suction if indicated
Talc pleurodesis (if >75% of visceral and parietal pleura in direct contact on CXR)

---

**Follow up**
At 10-14 days, then fortnightly for 8 weeks, then monthly to 6 months and three monthly to 12 months
= Out-patients assessment
(data collection, health questionnaires)
14. APPENDIX

14.1 Symptom and Quality of Life Questionnaires

**Modified EQ-5D**

Date: __/__/__  Patient’s trial ID: __________

By marking a score anywhere between 0 and 10 in the box provided, please indicate how you feel in each of the categories below. 10 is the best imaginable, and 0 the worst.

**Mobility:**

10 = no problems walking about
0 = confined to bed

**Self-Care:**

10 = I have no problems with self-care
0 = I am unable to wash and dress myself

**Usual Activities:** (e.g. work, housework, leisure activities)

10 = I am unlimited in my usual activities
0 = I am unable to undergo any of my usual activities

**Discomfort/Pain:**

10 = No discomfort at all
0 = The worst pain imaginable

**Anxiety/Depression:**

10 = I am not at all anxious or depressed
0 = I am extremely anxious or depressed
Visual Analogue Score (VAS)

Date:       /   /   . Patient’s Trial ID: 

To enable you to best describe how good or bad your shortness of breath and your quality of life is on a given day we have drawn a scale on which the best state you can imagine is marked 100, and the worst you can imagine is marked 0.

Please mark your shortness of breath score with an “S” and quality of life with a “Q” the day before (1), the day after (2), and every subsequent day for a week (3-8) after any procedure to drain your fluid. If you need more space please contact us. Once complete, please return this sheet in the envelope provided.
## AMPLE Summary of Protocol Changes

### Protocol v2 / 13.08.12

1. **Secondary Endpoints (Page 9)**
   We have set out the ‘Quality of Life’ endpoint to make clear that it is a distinct endpoint.

2. **Data Safety Monitoring Committee (Page 10)**
   The New Zealand (NZ) Ethics Committee requires all clinical trials to have a Data Safety Monitoring Committee (DSMC). Although this trial is comparing two standard clinical practices for the management of malignant pleural effusion, the use of indwelling pleural catheters (IPC) is quite novel for NZ. Following discussion with the Trial Steering Committee we have decided to convene a DSMC the details of which are entered into the protocol.

3. **Trial Flowchart (Page 16)**
   So as not to be prescriptive to clinicians in the size of chest drain used we have now provided a range of size 12 to size 18F. The Steering Committee also felt that this would avoid external reviewer criticism and provide some standardisation of the pleurodesis arm of the trial.

4. **Administrative Changes**
   There are page number changes and the version number and date of the protocol have been amended.

### Protocol v2 / 18.09.12

Following two anticipated deaths in the trial we have determined the need to further amend the trial protocol. The protocol changes are as follows:

1. **Trial Committees and Adverse Event Management (page 9)**
   We have further clarified the role of the DSMB with regards to Serious Adverse Events.

2. **Adverse Events (page 12-13)**
   This trial is recruiting participants who have life-limiting malignant disease and a percentage of these participants are anticipated to die due to disease progression during their time in the trial. Following discussion with the Steering Committee and with the SCGH Department of Research we have modified the protocol so that we will not report these anticipated deaths as Serious Adverse Events.

### Protocol v3 / 16.09.13

**Substantial Amendment / Changes to randomisation stratification (p9)**

With the addition of the National University of Singapore, under PI: Dr Pyng Lee, as a site and following extensive discussions with our independent Trial Steering Committee (TSC), it has been decided to alter the randomisation stratification. This is to minimise for the potential differences in length of hospital stay / admission threshold to accommodate clinical practice in Singapore.

The current stratification is for mesothelioma and trapped lung. Singapore vs the rest of the study sites will be added as a third stratification. Although we have recruited 40% of our target figure we do not believe that this change will alter the study results.

*To maintain allocation concealment, randomisation was performed in real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara). Initially, a minimisation program was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5-0.7 favouring the treatment that*
would minimise differences between groups on two key prognostic factors (mesothelioma and trapped lung). When Singapore was added as a site in late 2013, stratification by region (Australasia versus Singapore) was added because of differences in baseline characteristics (predominantly the prevalence of mesothelioma) between Australasia and Asia. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable (1).


Administrative Amendments

p3 / Updated email address for Prof YC Gary Lee.
p4 / Addition of non WA site details of site and PI.
p6 / Abbreviations List - Addition of SCGH and removal of IRB.
p8 / 2.2 Disease and patients studied – broadened definition of study sites
p10 / Secondary Endpoints - Reference to patient diary records altered to ‘participant data’.
p12 / 3.1.1 Independent Ethics Committee & 3.1.2 Patient Information and Informed Consent- References to Institutional Review Board (IRB) removed.
p18 / The participant Information Sheet and Consent Form has been removed from the protocol to make for easier document administration.
p18 & 19 / Titles of ‘Modified EQ-5D’ and ‘Visual Analogue Score’ added to the questionnaires.
<table>
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<th>Amendment</th>
<th>Amendment Type</th>
<th>Justification</th>
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<td>1</td>
<td>Protocol date and version no.</td>
<td>Administrative</td>
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<tr>
<td>2</td>
<td>Updated Prof Lee's email address</td>
<td>Administrative</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Addition of Dr Rajesh Thomas</td>
<td>Administrative</td>
<td>Dr Thomas is involved with this study in relation to his PhD under Prof Lee.</td>
</tr>
<tr>
<td>3</td>
<td>Addition of Kevin Murray</td>
<td>Administrative</td>
<td>Kevin Murray has had significant involvement especially in the writing up of the Statistical Analysis Plan.</td>
</tr>
<tr>
<td>3</td>
<td>Removal of Associate Investigators</td>
<td>Administrative</td>
<td>These can now be found on a separate Contacts List.</td>
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<tr>
<td>4</td>
<td>Updated Contents</td>
<td>Administrative</td>
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</tr>
<tr>
<td>6</td>
<td>Abbreviations updated</td>
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<td></td>
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<tr>
<td>8</td>
<td>2.2 Disease and patients studied – removal of site names.</td>
<td>Administrative</td>
<td>This is to make the protocol a more generic document.</td>
</tr>
<tr>
<td>9</td>
<td>2.3 Trial treatments – intervention and control – rewritten and improved wording.</td>
<td>Administrative</td>
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<tr>
<td>9</td>
<td>2.3.1 Bedside Talc pleurodesis – improved wording.</td>
<td>Administrative</td>
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<tr>
<td>9</td>
<td>2.3.2 IPC Management – improved wording.</td>
<td>Administrative</td>
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<tr>
<td>10</td>
<td>2.4 Randomisation – alteration of</td>
<td>Substantial</td>
<td>The randomisation process is different from the original planned</td>
</tr>
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The randomisation system used in this study is via a secure web based software system called Filemaker. This incorporates minimisation criteria for,

i) mesothelioma or non mesothelioma
ii) Australasian or other site
iii) trapped lung or not

To maintain allocation concealment, randomisation is performed in real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara). Initially, a minimisation program was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5-0.7 favouring the treatment that would minimise differences between groups on two key prognostic factors (mesothelioma and trapped lung). When Singapore was added as a site in late 2013, stratification by region (Australasia versus Asia) was added to account for any potential differences in baseline characteristics between patient and disease cohorts. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable.

10 Various minor changes in syntax. Administrative

11 Various minor changes in syntax. Administrative

12 **2.7 Trial Management Committees** Substantial

The Trial Steering Committee (TSC) and Data Safety Monitoring Committee are able to provide the necessary support and guidance.

Dr Rajesh Thomas has been added to the TSC.

12 **Recruitment Process** – additional section Substantial

This is an addition to the protocol to provide detail of the recruitment process.

13 **Statistical Plan – Missing Data** – Substantial

This is an addition to the protocol to state the process by which
<table>
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<th>additional section</th>
<th>missing data will be managed.</th>
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<td>13</td>
<td><strong>Sample Size Calculations</strong> – additional section</td>
<td>Substantial This is an addition to the protocol and outlines the process by which the recruitment targets were determined.</td>
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<td>20</td>
<td><strong>Flowchart - Removal of spirometry</strong></td>
<td>Administrative It is found on clinical practice that performing spirometry was difficult for participants; therefore removed as the spirometry results are not affecting any of the study outcomes.</td>
</tr>
<tr>
<td>21</td>
<td><strong>Symptom and Quality of Life Questionnaires - EQ-5D</strong></td>
<td>Administrative Questionnaire title added.</td>
</tr>
<tr>
<td>22</td>
<td><strong>Visual Analogue Score (VAS)</strong></td>
<td>Administrative Questionnaire title added and length of vertical lines corrected.</td>
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AMPLE

The Australasian Malignant Pleural Effusion Trial

A Multicentre Randomized Study Comparing Indwelling Pleural Catheter vs Talc Pleurodesis in Patients with Malignant Pleural Effusions

STATISTICAL ANALYSIS PLAN
Version 1 / 11.01.2015

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1. **BACKGROUND AND DESIGN**

The main characteristics of this trial have been summarised using AMPLE Protocol Version 4 (05.05.2014). Please refer to this protocol for full details.

1.1 **Trial Summary**

Malignant pleural effusion (MPE) affects ~8000 patients annually Australia-wide. It causes breathlessness and requires pleural interventions to manage the fluid accumulation.\(^1\) Standard of care involves in-patient drainage of the effusion and performing talc pleurodesis (instillation of talc intra-pleurally). This procedure fails in about 30% of patients (higher in the longer survivors).\(^2\) Upon failure, patients often require more pleural interventions to manage the recurrent effusion. Pleurodesis can be painful; can occasionally cause life threatening adverse events, and carries substantial healthcare costs. Hospitalisation for a pleurodesis procedure requires an average of 6 bed days.\(^2\) Considering that the average life expectancy for patients with this condition is just 3 to 9 months, it is crucial to reduce hospital admission time to maximise time spent with loved ones.

Ambulatory indwelling pleural catheters (IPC), an alternative FDA-approved treatment for MPE, may provide benefits over pleurodesis.\(^3\)\(^-\)\(^5\) Treatment is mainly as an outpatient where patient-controlled fluid drainage (by the patient or carer) avoids inpatient pleurodesis and its disadvantages. Our pilot data suggests that IPC is superior to pleurodesis in reducing the days patients need to spend in hospital in their remaining life span\(^6\). The protocol describes a randomised controlled trial to assess the need for hospital care days between patients with MPE treated with talc pleurodesis and those managed with IPC.

1.2 **Study Hypothesis**

Patients with MPE from malignant mesothelioma or other metastatic pleural cancers will require less hospitalisation if treated with IPC compared to talc pleurodesis.

1.3 **Study Objectives**

AMPLE is a randomised controlled trial of patients with MPE treated with either IPC or talc pleurodesis. The primary outcome is the total number of days, related to all causes, spent in hospital. Secondary outcomes include the number of inpatient care days specifically related to management of MPE, self-reported quality of life and breathlessness scores, and adverse
events. Comparison of the outcomes in the two arms will define whether ambulatory IPCs are superior to talc pleurodesis in keeping patients out of hospital, improving symptom control, and whether or not they are cost effective and safe.

If this trial is positive, it will directly improve care for one of the most common respiratory problems, to the benefit of ~15,000 patients each year in Australia.

1.4 Patient Eligibility Criteria

1.4.1 Inclusion Criteria

1. Patients must have a symptomatic MPE requiring intervention. The diagnosis is established through:

a) Histo-cytologically proven pleural malignancy or
b) Recurrent, large exudative pleural effusion with histologically proven cancer outside the thorax and no alternative cause.

2. Written informed consent.

1.4.2 Exclusion Criteria

1. Age < 18 years
2. Effusion smaller than 2cm at maximum depth
3. Expected survival <3 months
4. Chylothorax
5. Previous lobectomy or pneumonectomy on the side of the effusion
6. Previous attempted pleurodesis
7. Pleural infection
8. Total blood white cell count <1.0 x 10^9/l
9. Hypercapnic ventilatory failure
10. Patients who are pregnant or lactating
11. Irreversible bleeding diathesis
12. Irreversible visual impairment
13. Inability to give informed consent or comply with the protocol
1.5 Trial Intervention

1.5.1 Trial Treatments – intervention and control
Patients will be randomly assigned (1:1) to either an indwelling ambulatory pleural catheter or talc pleurodesis for the management of the malignant pleural effusion. All patients will complete self-reported quality of life and breathlessness scores. Adverse events and health care costs will be recorded to compare secondary outcomes.

1.5.2 Follow-Up
All patients will be followed up for 12 months or death, whichever is earlier. Patients will undergo outpatient assessment post-intervention at 10-14 days, then fortnightly for 8 weeks, monthly to 6 months, and three monthly to 12 months, or until death, whichever is earlier.

1.5.3 Randomisation
An independent specialist with expertise in trial statistics and randomization setup, who is not involved in the study, will manage the allocation sequence. To maintain treatment allocation concealment, eligible patients will be randomised in an equal ratio using a computer-derived allocation system that will be delivered real time by a web interface (Filemaker Server Advanced, Filemaker Inc., Santa Clara) c/o Prof Simon Brown, University of Western Australia. Randomisation will include minimisation with a probability of 80% by the following criteria:

1. Australasian centres vs centres outside Australasia
2. Histological tissue type (mesothelioma vs. non-mesothelioma) as survival is higher in mesothelioma compared to non-mesothelioma metastatic MPE, and the risk of catheter associated subcutaneous tumour invasion may be higher with mesothelioma;
3. The presence of trapped lung (since this has been postulated to reduce the likelihood of a successful pleurodesis).

Initially, a minimization program was used so that patients within Australia and New Zealand (Australasia) were allocated with a probability of 0.5-0.7 favoring the treatment that would minimize differences between groups on the two key prognostic factors; mesothelioma and trapped lung. Subsequently the Singapore and Hong Kong sites were approved to join the trial in late 2013 and mid-2014 respectively.

With the addition of Singapore and Hong Kong sites during the study, stratification by region (Australasia versus Asia) was added to minimize and address any potential differences in
patient ethnicity and incidence of cancers eg mesothelioma, and any variation in clinical practice. The probability favouring the treatment that would minimise bias was increased to 0.8 accordingly to compensate for this added variable.7

1.5.4 Figure 1 - AMLE Study Flowchart

**Trial Entry**
1. Symptomatic malignant pleural effusion requiring intervention. The diagnosis of MPE may be established by:
   a) Histo-cytologically proven pleural malignancy.
   or
   b) Recurrent, large exudative pleural effusion with histologically proven cancer outside the thorax and no alternative cause.
2. Fulfils inclusion criteria.
3. Written informed consent.

**Randomise**

- **Indwelling pleural catheter drainage**
  IPC insertion performed as an inpatient or day case procedure.

- **Talc Pleurodesis**
  - Admission to hospital.
  - 12-18F chest drain insertion. Pleural suction if indicated.
  - Talc pleurodesis (if >75% of visceral and parietal pleura are in direct contact on CXR).

**Follow up (Post-intervention)**
Outpatient/telephone assessment for data collection and completion of questionnaires,
- At 10-14 days,
- then fortnightly for 8 weeks,
- monthly to 6 months
- and 3 monthly to 12 months, or death, whichever is earlier.
In this pragmatic trial, the delivery of each of the therapies (talc pleurodesis or IPC) and aftercare will be provided by each centre according to their usual practice protocols, as there are no agreed best practice standards in the detailed delivery of these procedures. The local PI will be responsible for ensuring that properly trained doctors trained carry out, or supervise, the procedure. All patients will receive clinical care as otherwise recommended by their attending physicians. Any further pleural fluid management (e.g. if pleurodesis fails) or aftercare of IPC will be performed as per usual practice at the treating centre.

2. OUTCOME MEASURES

2.1 Primary Outcome Measure

2.1.1 The number of days spent in hospital (bed days) for all hospital admissions from any cause following intervention until death or the end of the study follow-up.

This primary endpoint was selected, as it is a meaningful outcome for cancer patients and their carers, and clinicians. We believe that for patients with malignant effusions who often have limited life expectancy, it is the reduction in the total number of days spent in hospitals, not just hospital days related to effusions, which is most meaningful.

Given the impossibility of blinding, hospital admissions, wherever possible, will be decided by the independent treating physicians, not by the study investigators. The reason(s) for admission must be documented and satisfy at least one of the following criteria:

a) A procedure is required that cannot be performed in the outpatient setting because of the need for >2 hours of close nursing or medical attention.

b) A coexisting or new medical problem requires inpatient therapy.

c) Cancer or effusion-related symptoms cannot be adequately controlled at home with community nursing, GP and outpatient clinic support.

The following criteria will be used to define the primary end-point:

a) The number of days spent in hospital is defined as the number of nights the patient is an inpatient at midnight (24:00).

b) Any hospital admission involving one or more days will be counted towards the primary outcome.
c) Day-case chemotherapy administration or day-case pleural interventions will not be included in the primary outcome. Hospital admission for inpatient chemotherapy or pleural procedures with stay extending beyond midnight will be counted towards the primary outcome.

d) Hospice care - All days in hospice will be counted as hospital bed days.

e) If a patient is an inpatient at the time of randomization, bed days will be counted only from the date of intervention (i.e. IPC insertion or insertion of ICC for talc pleurodesis). Days spent in hospital prior to the procedure will not be counted towards the primary outcome. Likewise if there was any delay between admission and the procedure, e.g. if admitted on a Monday but procedure cannot be done until Tuesday, the delay is not included.

An independent assessor, not related to the clinical trial, will assess the validity of the hospital admissions for its justification and duration.

During each study visit all patients will be questioned about all hospital admissions including hospitals other than the study site. All electronic databases and case records will also be scanned at the end of the study to capture all hospital admissions. Hospital admissions from all causes will be recorded.

2.2 Secondary Outcome Measures

2.2.1 The number of days spent in hospital (bed days) for hospital admissions from effusion-related causes following intervention until death or the end of the study follow-up.

Hospital admissions will be further categorized and days of admissions directly attributable to the pleural effusion and/or its treatment will be a secondary outcome recorded as “effusion-related”. The following criteria will be considered while defining effusion-related bed days:

a) Effusion-related admissions are defined as days and number of episodes for pleural effusion-related causes. This includes admissions for management of pleural effusion, and associated symptoms, pleural or related procedures and/or complications of a prior pleural procedure.

b) For every admission, a day-by-day assessment using the same rules is performed. Days that did not include a pleural procedure, management of a complication to previous pleural procedures or other treatment for effusion are considered “unrelated to pleural effusion”.
c) An incomplete day (not extending beyond midnight) in hospital for effusion-related cause, e.g. day procedure admission for IPC insertion or other drainage procedures will not be considered.

d) Pleural drainage in the outpatient setting, e.g. therapeutic thoracentesis, will not be considered as a bed day.

e) Hospice care - Hospice admissions, unless for the sole purpose of pleural drainage, will not be considered as effusion-related.

f) In the case of hospital admissions for management of both effusion-related and non effusion-related problems, the days required directly for effusion-related management will be considered as effusion-related bed-days.

Other hospital admissions (as defined above) will be captured from information provided by patients during each study visit and by scanning all electronic databases and case records.

2.2.2 The number of days spent in hospital (bed days), excluding hospice admissions, for all hospital admissions from any cause following intervention until death or the end of the study follow-up.

The data for the primary endpoint will also be analysed with days from hospice admissions excluded. This will provide informative data as hospice admission is often for terminal end-of-life care where the study intervention may not play a significant role in patient management. There may also be differences in practice between study sites in end-of-life care and the utilisation of hospice.

2.2.3 Survival and Adverse Events

Survival is defined as a binary variable for all cause mortality during the study period. Serious adverse events (SAEs) are defined to be events specifically related to the study intervention, as specified in the protocol.

2.2.4 Changes in Breathlessness Over Time

Breathlessness will be measured using a visual analogue score (VAS)\(^{3,8,9}\) on a 1-100mm scale (to the nearest mm). Lower scores indicate more breathlessness. This will be recorded at baseline and day 1 post-intervention, self-reported daily for the first 2 weeks, and subsequently at study visit intervals until either death or completion of follow-up.

The VAS scoring will be performed by at least one observer blinded to the patient and treatment intervention. The average breathlessness score will be calculated using all VAS
measurements self-reported daily from intervention until day 14, fortnightly for 8 weeks, monthly to 6 months and three monthly to 12 months, or death.

2.2.5 Changes in Quality of Life (QOL) Over Time

A secondary outcome analysis will be performed to assess how quality of life (QOL) changes over time from enrolment until study completion or death. QOL will be measured using 2 separate instruments:

a) A visual analogue score (VAS)\textsuperscript{3,8,10} on a 1-100mm scale (to the nearest mm) recorded pre and post study intervention, then self-reported daily for the first 2 weeks, and subsequently at every study visit intervals until either death or completion of follow-up. Lower scores indicate poorer QOL.

b) The modified EQ-5D questionnaire completed before the study intervention, at 8 days post-study intervention, then self-reported at every study visit intervals until either death or completion of follow-up.

The average QOL score will be calculated using,

a) All VAS measurements from pleural intervention until day 14, 4 weeks, 3 months, 6 months and 12 months, or death.

b) All modified EQ-5D scores from pleural intervention until day 8, 10-14 days, then fortnightly for 8 weeks, monthly to 6 months and three monthly to 12 months or death.

In the event that the VAS scale had minor variations in length from photocopy or PDF conversions, the exact length of the scale was measured and expressed as a proportion to 100mm by the independent assessors.

2.2.6 Further Pleural Intervention

Patients randomised to the pleurodesis arm and IPC arm will be classified as a complete pleurodesis failure or IPC failure respectively if they need to undergo further pleural intervention for relief of breathlessness on the same side as their pleurodesis or IPC during the study period. Patients randomised to the pleurodesis arm where there is clinical or radiological recurrence of pleural effusion without a need for further pleural intervention will be classified as partial failure of pleurodesis as per ATS/ERS criteria\textsuperscript{11}.

Given the impossibility of blinding, further pleural interventions will be decided by independent treating physicians unrelated to the study, wherever possible. The reason(s) for
further pleural intervention will be documented for management of a recurrent same-sided pleural effusion, without an alternative cause, in a symptomatic patient.

3. SAMPLE SIZE

We have provided an estimate of sample size based on our pilot non-randomized study\(^6\) that showed that those (n=34) who chose IPC spent a median of 6.5 days (IQR, 3.75-13.0d) compared to 18.0 days (IQR, 8.0-26.0d) (p=0.002) in the talc group (n=31). This takes into consideration that the primary response data is likely to be highly skewed, and hence a non-parametric test would be more appropriate.

In order to examine the potential benefit of reduction in hospital stay using IPC, we estimate 65 patients in each group are needed to be able (with 80% power and \(\alpha = 0.05\)) to detect a difference between groups of an improvement of 5 or more total days in time spent in hospital, based on preliminary estimates of 18 days post-pleurodesis and standard deviation of 9.3. Allowing for a lost-to-follow-up rate of 12%, 73 patients per group will be needed, to make a total recruitment target of 146. This is a conservative estimate as no patient was lost to follow-up in the pilot study.

4. OUTCOME ANALYSIS

4.1 Analysis Principles

All outcomes will be analysed for superiority. Superiority analyses will be two-sided, and considered statistically significant at the 5% level. Unless otherwise stated, all analyses will be adjusted for the following minimisation variables - histological tissue type (mesothelioma vs. non-mesothelioma); trapped lung (presence vs. absence of trapped lung); and recruitment sites (Australasian centres vs. centres outside Australasia). Mean imputation will be used during analyses to adjust for missing values of baseline variables.

4.2 Analysis

All analyses will be conducted on both an intention-to-treat (ITT) and per-protocol (PP) basis. The ITT sample is defined as all randomized subjects including those who are lost to follow-up or have missing data. If the patient did not receive the assigned intervention post-randomisation, the patient will still be included in the ITT sample and analyzed according to
randomized assigned treatment group. The per-protocol sample is defined as all randomized subjects who fulfilled the eligibility criteria, received the correct treatment assignment according to randomization schedule, and followed the protocol. According to the protocol, hospital admissions, adverse events, change in VAS score of breathlessness, change in VAS and modified EQ-5D scores for QOL, and further pleural interventions are recorded during each study visit (initially within 2 weeks followed by 4 weeks, 3 months, 6 months and 12 months, or death.

Due to the multi-center design of the study, additional analyses for all primary and secondary outcomes will include appropriate center adjustments.

Demographics will be presented and compared between the two groups. Variables will include age, gender, side of effusion requiring intervention, effusion size, type of underlying malignancy, presence of trapped lung and ECOG status. Primary and secondary outcomes will be analysed as described below.

4.2.1 Primary Outcomes

4.2.1.1 The total bed days for all hospital admissions from any cause following intervention.

The total bed days for all hospital admissions will be analysed initially using a Mann Whitney non-parametric test to compare the two treatment arms. Subsequent supporting analyses will be carried out using a negative binomial model with adjustments made for actual length of follow up (accounting for death and withdrawals) and important covariates.

4.2.2 Secondary outcomes

4.2.2.1 Effusion-related bed days for hospital admissions following intervention.

The total effusion-related bed days for hospital admissions will be analysed similarly to the primary outcome variable.

4.2.2.2 The total bed days for all hospital admissions, excluding hospice admissions, from any cause following intervention.

The total bed days for hospital admission, excluding hospice admissions, will be analysed similarly to the primary outcome variable.
4.2.2.3 Survival and Adverse Events

Survival
Kaplan Meier curves and log rank tests will be carried out to analyze time to death and serious adverse events. Subsequent supporting analyses will be carried out using Cox proportional hazards models to examine adjustments for important covariates. Individuals who did not experience an event will be censored at the end of the follow-up period of the study. Individuals withdrawn from the study early or lost to follow up will be censored at the date of withdrawal or the last contact visit respectively. For adverse events only individuals who die during the follow up period will be treated as censored at this time point.

In addition the frequencies of serious adverse events will be compared between the intervention groups using Fisher’s exact tests.

Adverse Events
Safety will be evaluated by tabulation of adverse events and will be presented with descriptive statistics at baseline and follow-up visits for each treatment group. With each SAE the study investigator will determine the intensity and causality as per ICH GCP guidelines. All SAEs are discussed at the Data Safety Monitoring Committee meetings to reach a consensus on causality. If this differs from the original decision the local ethics committee is informed.

In patients with bilateral pleural effusions, an attempt will be made to separate adverse events by side. Adverse events related to the randomization side will be documented separately from those related to the effusion on the opposite side, or its treatment. However, all admissions, even if related to the opposite side will be counted towards the treatment arm. Failure of pleurodesis will be separately recorded and considered as an adverse event if further pleural intervention is required. Similarly, failure of IPC to relieve symptoms and necessitating further pleural intervention will be recorded as an adverse event. The number and proportion of patients experiencing at least one AE, and the number and proportion of patients experiencing at least one SAE will be presented descriptively. The mean number of AEs and SAEs per patient will be presented.

4.2.2.4 Change in Breathlessness (SOB) Over Time following Intervention

VAS scores for breathlessness$^{12}$ will be analysed using linear mixed effects models, including fixed effects of time, treatment group and time by treatment group interaction as appropriate
and random effects of individual. An appropriate correlation structure for the errors will be incorporated. An absolute difference in mean VAS scores of >10mm compared to baseline scores will be considered clinically relevant.

4.2.2.5 Changes in Quality of Life QOL Over Time following Intervention

VAS scores for QOL and modified EQ-5D scores for QOL will be analysed using linear mixed effects models including fixed effects of time, treatment group and time by treatment group interaction as appropriate and random effects of individual. An appropriate correlation structure for the errors will be incorporated.

The minimally important difference (MID) is defined as one-half SD of the baseline. The patient’s QoL was considered to have improved if at least one post-procedure score was > 1 MID above his/her own baseline, and if no other post-procedure score fell below the baseline. A drop of any score by > 1 MID below the patient’s baseline, regardless of his/her other scores, was considered deterioration.

4.2.2.6 Further Pleural Intervention

Kaplan Meier curves and log rank tests will be carried out to analyze time to further pleural intervention. Subsequent supporting analyses will be carried out using Cox proportional hazards models to examine adjustments for important covariates. Individuals withdrawn from the study early or lost to follow up will be censored at the date of withdrawal or the last contact visit respectively.

In addition the frequencies of further pleural intervention will be compared between the intervention groups using Fisher’s exact tests. Patients with no recorded follow-up data on pleurodesis or IPC failure status will not be included in the analysis.
**Suggested Template for Tables**

**Table 1 - Baseline Demographics**

<table>
<thead>
<tr>
<th></th>
<th>Talc Pleurodesis (n=…)</th>
<th>Indwelling Pleural Catheter (n=…)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, No. (%)</td>
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<tr>
<td>Age (y)</td>
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<tr>
<td>Female, No. (%)</td>
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<td>Right side, No. (%)</td>
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<tr>
<td>Type of primary malignancy, No. (%)</td>
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<tr>
<td>Mesothelioma</td>
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<tr>
<td>Non-mesothelioma</td>
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<tr>
<td>Lung</td>
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<td>Breast</td>
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<tr>
<td>Others</td>
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<tr>
<td>Trapped lung, No. (%)</td>
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<td>ECOG, No. (%)</td>
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<td>2</td>
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<td>3-4</td>
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<tr>
<td>Effusion size, No. (%)</td>
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<tr>
<td>Small (1-2)</td>
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<tr>
<td>Moderate (3-4)</td>
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<tr>
<td>Large (5)</td>
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<tr>
<td>No. of previous thoracentesis, No (%)</td>
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<td></td>
</tr>
<tr>
<td>1-3</td>
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<td>4-6</td>
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<tr>
<td>&gt; 6</td>
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<tr>
<td>VAS dyspnoea (mm)</td>
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<tr>
<td>VAS QOL (mm)</td>
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<tr>
<td>Modified EQ-5D QOL</td>
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</tbody>
</table>
Table 2 – Summary Statistics for Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Talc Pleurodesis (n=…)</th>
<th>Indwelling Pleural Catheter (n=…)</th>
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</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
<td></td>
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<tr>
<td>Total hospital stay (d)</td>
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<tr>
<td><strong>Secondary Outcomes</strong></td>
<td></td>
<td></td>
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<tr>
<td>Effusion-related hospital stay (d)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Survival</strong></td>
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<td></td>
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<tr>
<td>All-cause mortality at 6 months, n (%)</td>
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<tr>
<td>All-cause mortality at 12 months, n (%)</td>
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<tr>
<td>Time from intervention to death/last follow-up</td>
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<tr>
<td><strong>Safety</strong></td>
<td></td>
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<tr>
<td>SAE, n (%)</td>
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<tr>
<td><strong>Breathlessness Scores</strong></td>
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<tr>
<td>VAS dyspnoea (mm) at 4 weeks</td>
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<tr>
<td>VAS dyspnoea (mm) at 3 months</td>
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<tr>
<td>VAS dyspnoea (mm) at 6 months</td>
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<tr>
<td>VAS dyspnoea (mm) at 12 months</td>
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<tr>
<td><strong>QOL Scores</strong></td>
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<tr>
<td>VAS QOL (mm) at 4 weeks</td>
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<td>VAS QOL (mm) at 3 months</td>
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<td>VAS QOL (mm) at 6 months</td>
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<td>VAS QOL (mm) at 12 months</td>
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<tr>
<td>Modified EQ-5D QOL at 4 weeks</td>
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<td>Modified EQ-5D QOL at 3 months</td>
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<td>Modified EQ-5D QOL at 6 months</td>
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<tr>
<td>Modified EQ-5D QOL at 12 months</td>
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<tr>
<td><strong>Further pleural intervention</strong></td>
<td></td>
<td></td>
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<tr>
<td>Failure of pleurodesis/ IPC at 4 weeks, n</td>
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<td></td>
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<tr>
<td>Failure of pleurodesis/ IPC at 3 months, n</td>
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<tr>
<td>Failure of pleurodesis/ IPC at 6 months, n</td>
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<tr>
<td>Failure of pleurodesis/ IPC at 12 months, n</td>
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<tr>
<td>Time from intervention to treatment failure (d)</td>
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<tr>
<td>No. of pleural procedures required post-treatment failure</td>
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<td></td>
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</tbody>
</table>
REFERENCES