



Government of Western Australia  
Department of Health  
Sir Charles Gairdner Hospital



Department of Respiratory Medicine  
Ground Floor B Block  
Telephone: 61 8 6457 1754  
<http://Pleura.com.au>

**The Australasian Malignant Pleural Effusion (AMPLE)-4 Trial:  
Topical Antibiotic Prophylaxis for Infections of Indwelling Pleural Catheters in  
Patients with Malignant Pleural Effusions**

version 1.00 / 27.07.22

Sir Charles Gairdner & Osborne Park Health Care Group  
Human Research Ethics Committee RGS:

CPI: Prof Y C Gary Lee MBChB PhD FCCP FRCP FRACP  
Professor of Respiratory Medicine, University of Western Australia  
Consultant & Director of Pleural Services, Respiratory Dept, Sir Charles Gairdner  
Hospital  
Head, Pleural Medicine Unit, Institute for Respiratory Health  
NH&MRC Career Development Fellow  
  
UWA School of Medicine  
533 Harry Perkins Building  
QE II Medical Centre  
Perth WA 6009

Lead Centre: Sir Charles Gairdner Hospital, Hospital Ave  
Nedlands, Western Australia

CPI Signature:

## WA HEALTH RESEARCH PROTOCOL

### Australasian Malignant Pleural Effusion Trial - 4

Trial Details	
<b>Protocol/Clinical Trial Title:</b>	<b>AMPLE-4: Topical Antibiotic Prophylaxis for Infections of Indwelling Pleural Catheters in Patients with Malignant Pleural Effusions</b>
<b>Short Title</b>	<b>AMPLE-4: Topical Mupirocin Prophylaxis for Infections of Indwelling Pleural Catheters</b>
<b>Protocol Number (Version and Date):</b>	Version 1.00 / 27.07.22
<b>Coordinating Principal Investigator Name:</b>	Prof Y C Gary Lee
<b>Coordinating Principal Investigator Contact Details:</b>	UWA School of Medicine 533, Harry Perkins Building QE II Medical Centre Perth, WA 6009, Australia Tel: +61 8 61510913

#### Amendment History

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Amendment no.	Protocol version no.	Date Issued	Author of Changes	Change details
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## **Abbreviations**

AI	Associate Investigator
AE	Adverse Event
CPI	Coordinating Principal Investigator
CRP	C Reactive Protein
CRF	Case Report Forms
CXR	Chest xray
DSMC	Data Safety and Monitoring Committee
ECOG	Eastern Co-operative Oncology Group
ESI	Exit Site Infections
GCP	Good Clinical Practice
ICH	International Council for Harmonisation
IPC	Indwelling Pleural Catheter
MPE	Malignant Pleural Effusion
NHMRC	National Health and Medical Research Council
PD	Peritoneal Dialysis
PI	Principal Investigator
PICF	Participant Information and Consent Form
QoL	Quality of Life
RCT	Randomised Controlled Trial
SAE	Serious Adverse Event
TSC	Trial Steering Committee
UIN	Unique Individual Number

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## 1. Summary

### 1.1 Trial Summary

Malignant Pleural Effusion (MPE) can complicate most cancers and commonly causes disabling breathlessness and impairs quality of life (QoL). Therefore, the goal of management is to provide effective control of the symptoms with minimal interventions.

Indwelling pleural catheter (IPC) is an ambulatory drainage device for MPE. Randomised studies have proven that IPC is significantly superior to talc slurry pleurodesis in reducing need for invasive pleural interventions and hospital stays whilst providing equivalent benefits in QoL and breathlessness.

IPC-related infections remain a concern for clinicians, particularly in patients eligible for chemotherapy. The incidences of IPC-related infections (of the pleural fluid, catheter tract and skin) vary among series, and their management is heterogenous.<sup>1</sup> IPC-related infections often require hospitalisation and delay oncological treatments. Effective strategies to prevent IPC-related infection will significantly enhance IPC use worldwide.

Care of IPC shares significant similarities with that of peritoneal dialysis (PD) catheters, and infection (especially PD peritonitis) is likewise a major burden for PD programs. Topical antibiotics prophylaxis has recently been shown in several trials to significantly reduce PD catheter-related infections, informing clinical care/guidelines.

The **Australasian Malignant Pleural Effusion (AMPLE) trial-4** is a multicentre RCT that will evaluate the use of regular prophylactic topical mupirocin (vs no antibiotics) to reduce catheter-related infections in patients fitted with an IPC for malignant fluid drainage. Mupirocin is a topical antibiotic used worldwide for 25 years with a strong safety record. Primary outcome is the proportion of patients who developed a catheter-related (pleural, tract or skin) infection from catheter insertion until death (or 6-month follow up). Secondary outcomes include infection rates adjusted for days of catheter *in situ*, infection-related hospitalisation (episodes and days), treatment acceptability for patients, complications and survival.

## 2. Rationale / Background

### 2.1 Background

Malignant pleural effusion affects over 8,000 Australians and 1 million people worldwide each year.<sup>2</sup> Development of MPE generally heralds advanced incurable cancer. MPE can complicate most cancers, including 30% of breast and lung cancer and more than 90% of malignant pleural mesotheliomas.<sup>3</sup> The resultant breathlessness is disabling and significantly impairs quality of life (QoL). The key goals of management are to relieve breathlessness and enable physical activity while minimising interventions and time spent in hospital, in a cost-effective manner.

In our longitudinal study of 789 patients with MPE from Australia, UK and the Netherlands, survival ranged from 13 to 484 days<sup>4</sup> and depended on multiple factors including performance status and cancer type. MPE contributes to 126,825 hospital admissions a year in the USA with a median length of stay of 5.5 days, an 11% inpatient mortality and an annual inpatient care cost of US\$5 billion.<sup>5</sup>

Pleural drainages are invasive, painful, costly and require medical visits or hospitalisations, depriving patients of precious time in their limited lifespan. Pleurodesis, often attempted, has poor success

rates (<70%)<sup>6,7</sup> even in clinical trials with selected patients, is associated with severe pain (and fever) and involves hospitalisation of 5-6 days.

Indwelling Pleural Catheter (IPC) is an ambulatory drainage device for patients with MPE that permits evacuation of the fluid at home. A tunneled catheter is sited and patients (and/or their carers) are educated in home drainage. Multiple prospective and randomised studies have established IPC as superior to conventional talc slurry pleurodesis.

Advantages of IPC include a reduced re-intervention rate for symptomatic pleural fluid re-accumulation. Two studies have focused on re-intervention following IPC and demonstrated rates of 2 – 6%.<sup>8,9</sup> IPC is also associated with a reduction in hospital days vs talc slurry pleurodesis.<sup>9,10</sup> One non-randomised prospective study demonstrated a reduction in median hospital stay from 10.1 days post-VATS to 5.9 days with IPC, which was associated with a cost saving of \$7000 USD.<sup>11</sup> Moreover, IPC provided equivalent benefits in relieving breathlessness and chest pain compared with talc pleurodesis in two randomized trials.<sup>9,12</sup>

Despite the advantages of IPCs, it still has a 10-20% associated complication rate.<sup>13</sup> The largest multi-centre series on IPC-related pleural infection,<sup>1</sup> found *Staphylococcus aureus* as the most common (~50%) causative organism, though the remaining cases involved a wide range of bacteria. Although the mortality was low (0.3%), most (74%) cases required hospitalisation and may require catheter removal for infection control.

IPC infections usually develop more than 6 weeks post-insertion<sup>14</sup> and include infections of pleural cavity/fluid, the tunnel tract (soft tissue) and skin at the exit site. Reported incidences of IPC infections varied and was as high as 25% in the TIME-2 RCT<sup>9</sup> and 14.9% in the AMPLE-2 trial<sup>15</sup>. A systematic review also found that 3.4% of patients had skin infections.<sup>16</sup> Overall, 8.5% of patients had their IPCs removed to control infections.<sup>16</sup> Delay in chemotherapy because of IPC infection is well documented.<sup>17</sup>

Concerns of IPC infections have led different professional groups, such as the American Association of Bronchology & Interventional Pulmonology and the Intervention Pulmonology Outcome Group, to issue guidelines and consensus statement on practical aspects of IPC care, especially infection management.<sup>14,18</sup> Infection remains clinicians' biggest hesitation in adopting IPC use. No studies have investigated strategies for long term prevention of IPC-related infections.

IPCs share many similarities with peritoneal dialysis (PD) catheters which are also frequently complicated by peritonitis and exit site infections (ESIs). Use of topical antibiotics (especially mupirocin) to reduce PD related infections have been a subject of several recent studies. Mupirocin, as an antibiotic cream or ointment, has excellent activity against gram-positive organisms and is attractive as a prophylactic option against *S. aureus*-related infections.<sup>19</sup>

Significant reduction in peritonitis and ESIs attributed to *S. aureus* or Gram-positive organisms have been found in several studies when mupirocin was applied around the catheter exit-site.<sup>20-24</sup> A meta-analysis<sup>25</sup> found that mupirocin prophylaxis reduced the rate of *S. aureus* ESIs and peritonitis by 62% and 66% respectively. In a prospective controlled study,<sup>26</sup> mupirocin reduced the overall incidence of peritonitis by 61% and ESI by 55%. Specifically, *S. aureus* peritonitis was cut by 100% and ESI by 65%. Mupirocin was more effective when applied thrice-a-week (vs weekly) in preventing peritonitis and ESIs.<sup>27,28</sup> The International Society for Peritoneal Dialysis (ISPD) guidelines recommend daily application of topical antibiotic prophylaxis for peritoneal dialysis patients.<sup>29,30</sup>

No long-term preventive approaches currently exist for IPC-related infections, which are significant events to cancer patients and delay oncologic treatments. Management of infection require

hospitalisations with associated costs and 'rob' patients with advanced cancers of valuable time from home/family. The AMPLE-4 trial aims to move towards active prevention of IPC-related infections.

### 3. Trial Aims

This is a randomised controlled trial aiming to evaluate the use of regular prophylactic topical mupirocin (vs no antibiotics) to reduce catheter-related infections in patients fitted with an IPC for malignant fluid drainage.

### 4. Trial Design

#### 4.1 Primary endpoints and secondary endpoints

The Australasian Malignant Pleural Effusion (AMPLE) trial-4 is a pragmatic, multi-centre, open-labelled, randomised study. Four hundred and nineteen patients with MPEs, who require an IPC will be randomised 1:1 to either topical mupirocin or no topical mupirocin (standard care). MPE is defined as an effusion in which cancer cells are identified in the fluid or pleural biopsy; or is a large exudative effusion without other causes in a patient with advanced disseminated malignancy. Minimisation for i) cancer type (mesothelioma vs non-mesothelioma); ii) known presence of trapped lung (vs not); iii) ECOG performance status ( $\leq 2$  vs  $\geq 3$ ) and iv) current immunosuppression (or chemotherapy) vs not.

**Primary endpoint:** The primary outcome is the percentage of patients who developed an IPC-related infection from catheter insertion until death, or end of 6-month follow-up. IPC-related infection can be any one of the followings:

- Pleural infection: presence of pus and/or bacteria (by Gram stain or culture) in pleural fluid plus clinical picture compatible with infection (eg fever, leucocytosis, raised inflammatory markers).
- Catheter tract infection: signs of inflammation along the tract usually with swelling and significant tenderness plus clinical presentation compatible with infection.
- Cellulitis at exit site: signs of inflammation clinically warranting systemic antibiotic treatment as determined by the attending physician.

#### **Secondary endpoints:**

- i) Analysis of **Infection**
- ii) Analysis of **Hospital days**
- iii) **Adverse and serious adverse events**
- iv) **Resource utilisation**
- v) **Survival**

#### 4.2 Study type

This is a prospective (non-blinded) randomised controlled trial.

#### 4.3 Randomisation process and minimisation

The NHMRC Clinical Trials Centre will manage randomisation, which will be available 24 hours per day. Automatic randomisation following the entry of baseline and minimisation data will be confirmed by emails sent to the enrolling and the lead sites.

#### 4.9 Termination of the trial

Early trial termination may occur for the following reasons,



- a. The independent study Data Safety and Monitoring Committee have significant safety concerns that they raise with the Steering Committee advising early trial termination. This can be preceded by a period of no enrolment at the site whilst investigation of the safety issues is conducted.
- b. Alterations in accepted clinical practice making the continuation of the clinical trial untenable.

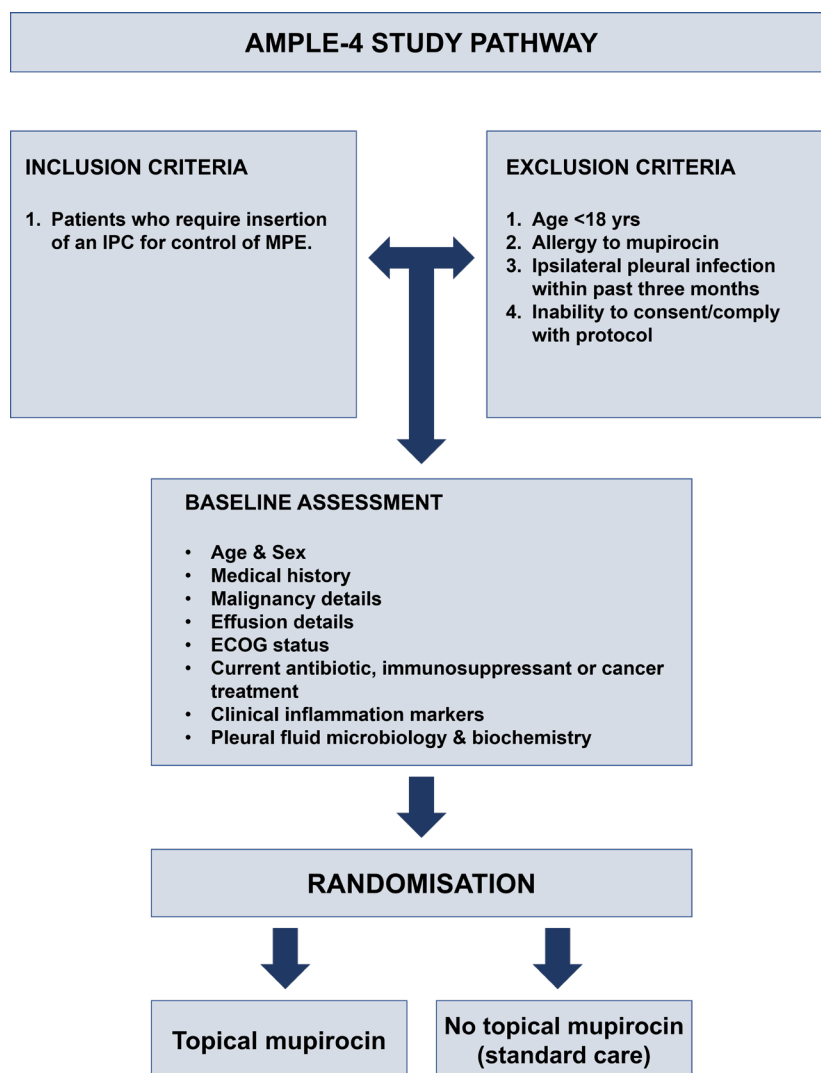
#### 4.10 Case Report Forms as source data

The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and will be considered to be source data.

#### 4.11 Trial Steering Committee (TSC)

The Trial Steering Committee will be responsible for the supervision of the trial in all its aspects. It will be responsible for ensuring the completion of the trial to clinical and ethical standards. It will monitor site recruitment and review any recommendations received from the DSMC.

**AMPLE-4 Flowchart 1 – Screening to Randomisation Arm**



## AMPLE-4 Flowchart 2 – Randomisation Arm Follow-up

	Topical mupirocin	No topical mupirocin (standard care)
T0	IPC insertion	IPC insertion
T1	Normal standard care for IPC dressing change PLUS topical mupirocin application	Normal standard care for IPC dressing change without topical mupirocin application
WEEKLY PHONE CALLS OR F2F FOLLOW/UPS POST DISCHARGE UP TO 6 MONTHS OR DEATH	<ul style="list-style-type: none"> <li>• Complete questionnaires</li> <li>• Pleural fluid microbiology if samples are collected</li> </ul>	<ul style="list-style-type: none"> <li>• Complete questionnaires</li> <li>• Pleural fluid microbiology if samples are collected</li> </ul>
IF IPC IS REMOVED (MONTHLY FOLLOW/UPS)	Assess for any long-term issues	Assess for any long-term issues

## 5. Source and Selection of Participants

### 5.1 Participant Screening and Selection

The site PI or designated site research staff (as per the Delegation Log) will screen patients with symptomatic MPE for when an IPC is planned for treatment. Potential participants will be approached about the study including inpatients under the clinical team and outpatients attending the outpatient clinics. Potential participants will be provided with the participant information and consent form (PICF) to read and given time to ask questions to the study team. They will also be given time to discuss the study with family and carers and their GP. Consecutive eligible participants will be offered trial entry and will be enrolled after providing informed consent. The site PI will be aware of their dual role as the patients' primary physician and as a clinical researcher and where this patient dependency can be a potential conflict. Enrolment and screening logs will be maintained and sites will send de-identified logs to the lead site at the beginning of every month.

### 5.2 Participant inclusion criteria

1. Patients who require insertion of an IPC for control of MPE°.

°MPE is defined as an effusion in which cancer cells are identified in the fluid or pleural biopsy; or is a large exudative effusion without other causes in a patient with advanced disseminated malignancy.

### 5.3 Participant exclusion criteria

1. Age <18 yrs
2. Allergy to mupirocin
3. Ipsilateral pleural infection within past three months

4. Inability to consent
5. Inability to comply with the protocol.

#### **5.4 Participant withdrawal criteria**

- a. Participants can withdraw at any time from the study and do not need to provide the research staff with a reason.
- b. We will retain all participant data up until the time of withdrawal as outlined in the PICF. There may be reasons for the site PI to decide to withdraw a participant from the study. This could be due to inability to comply with the study protocol such as availability for follow-ups or for other compliance issues. A participant may also be withdrawn in their best interests. In all cases, the study withdrawal form will be completed and a copy submitted to the lead site.
- c. Withdrawn participants will not be replaced.
- d. Where considered clinically necessary, withdrawn participants will be asked to return to clinic for a safety follow up appointment.

## 6. Treatment of Participants

### 6.1 Treatment description

Participants will be randomly assigned (1:1) to either:

#### a. Topical mupirocin

Topical mupirocin 2% cream will be applied around the exit-site of the IPC for an area approximating a 50 cents coin. An information sheet with a picture of how to apply the cream will be provided to patients/carers. The antibiotics should be applied after each drainage but at least twice weekly (with dressing change) even if draining less frequently. Mupirocin is a topical antibiotic used worldwide for decades with a strong safety record. It binds specifically to bacterial isoleucyl transfer-RNA synthetase and inhibits bacterial protein synthesis. It has a high level of activity against Gram-positive aerobes (eg Staphylococci and Streptococci) and some Gram-negative aerobes. Mupirocin, applied topically, has insignificant systemic absorption and, even if absorbed through broken skin, is rapidly metabolised in the liver and renally excreted.

#### b. No topical mupirocin (standard care)

Patients will be managed in the conventional manner with the usual education and care of the IPC, and without topical mupirocin prophylaxis. We have elected not to use placebo as a layer of ointment itself can potentially increase risks of infection and confound outcomes.

#### Standard Care

Participants in both arms will be managed by their own clinical teams and receive all other medical treatments (including chemotherapy and radiotherapy) as deemed clinically appropriate. Patients' medical care, including IPC care, oncology management etc, will be directed by their attending physicians, as per standard practice in the treatment hospital, regardless of study group allocation. This includes the frequency of drainage, drainage device (suction bottle or drainage bag), administration of talc pleurodesis via IPC, etc. All patients will receive standard education on IPC aftercare, have access to support services (eg direct phone line) and standard care from their attending physicians, eg chemo-irradiation and immunotherapy. Decision of IPC removal is made by the physicians in-charge. Generally, IPC can be removed if drainage is <50mL on 3 consecutive drainages and there is no significant fluid accumulation on imaging. All participants and carers will have the support and care of the respiratory unit. They will have access to the respiratory research staff via a direct phone line should any concerns arise.

### 6.2 Usual medications

Participants will be able to take their usual medications during the study.

### 6.3 Monitoring participant compliance / Study visits

Potential participants, as part of the informed consent process, will have the study procedures and follow-up plan discussed in detail with an emphasis placed on the need for follow-up availabilities.

All patients (or their carers) will be contacted by phone every week to assess for clinical outcomes (esp if developed any infections), compliance or adverse events until death or end of 6-month trial period. These phone calls will take ~5 minutes only and are generally welcomed by patients (providing a regular dialog with the hospital-based team). Frequency of the phone review will decrease to monthly once the IPC is removed. If the patient is attending hospital visits for other reasons, then the telephone review may be replaced by face-to-face assessment.

Where participants do not answer follow-up calls/attend planned study visits, the research staff will contact them again or book an additional visit if required. If the participant misses a visit due to an admission to the site hospital, the visit will be carried out in the hospital providing the participant is well enough.

## 7. Assessment of Efficacy

### 7.1 Specification of efficacy parameters

#### Primary Endpoint

The primary outcome is the percentage of patients who developed an IPC-related infection from catheter insertion until death, or end of 6-month follow-up. IPC-related infection can be any one of the followings:

- Pleural infection: presence of pus and/or bacteria (by Gram stain or culture) in pleural fluid plus clinical picture compatible with infection (eg fever, leucocytosis, raised inflammatory markers).
- Catheter tract infection: signs of inflammation along the tract usually with swelling and significant tenderness plus clinical presentation compatible with infection.
- Cellulitis at exit site: signs of inflammation clinically warranting systemic antibiotic treatment as determined by the attending physician.

#### Secondary Endpoints

- a. **Infection** will also be analysed
  - as the total number of episodes for all patients in each group
  - as percentage of patients and as total number of episodes – each adjusted for number of days IPC is *in situ* for each patient
  - as each of the individual types of infection
  - time to first episode of infection
  - for organism(s) causing infection (eg *S aureus* vs *others*).
- b. **Hospital days** will be analysed
  - as total days in hospital (for any reasons)
  - as days related to IPC-related infections, similar to methods used in prior AMPLE trials.<sup>12,15</sup> All records of hospitalisation will be reviewed by an independent investigator.
- c. **Adverse and serious adverse events** will be recorded as in previous AMPLE trials.<sup>12,15</sup>
- d. **Resource utilisation**: Resource use associated with antibiotics use, and that associated with IPC-related infections will be obtained from discharge letters and HIPE coding. In-/out-patient management of any related complications will be captured from hospital records or self-reports from patients and will include treatments, imaging and other interventions related to the adverse events. An experienced health economist, will oversee this study aspect.
- e. **Survival** will be measured from randomisation to death or end of study follow-up.

## 7.2 Schedule of treatment for each visit and follow up procedures

Topical Mupirocin Arm	
Baseline	Demographics and medical history Inflammatory markers* Pleural fluid analyses RANDOMISATION
Day 0 / INDEX procedure	IPC insertion as per local practice
Day 1 post-procedure	Evaluation of exit-site and application of topical mupirocin with dressing change
Day of discharge	Topical mupirocin supplied to patient Follow-up in clinic (if appropriate) arranged Appropriate education for person responsible for IPC drainage and dressing change (carer/home nurse)
Weekly follow-up up to 6 months**	<u>Either</u> : Phone calls <u>or</u> clinic visit Questionnaire (information on person carrying out drainage/dressing change, volume of drainage, frequency of drainage and dressing change (mupirocin application), any missed doses including reasons for missed doses, side-effects and IPC patency. Evaluation of exit-site and pleural fluid culture testing (if clinic visit).  <u>After IPC removal</u> Follow-up for any issues after IPC removal.

\* Inflammatory markers include WCC and CRP.

\*\* Monthly follow-up if IPC is removed

No Topical Mupirocin (Standard Care) Arm	
Baseline	Demographics and medical history Inflammatory markers* Pleural fluid analyses RANDOMISATION
Day 0 / INDEX procedure	IPC insertion as per local practice
Day 1 post-procedure	Evaluation of exit-site and dressing change (standard care)
Day of discharge	Follow-up in clinic (if appropriate) arranged Appropriate education for person responsible for IPC drainage and dressing change (carer/home nurse)
Weekly follow-up up to 6 months**	<u>Either</u> : Phone calls <u>or</u> clinic visit Questionnaire (information on person carrying out drainage/dressing change, volume of drainage, frequency of drainage and dressing change and IPC patency. Evaluation of exit-site and pleural fluid culture testing (if clinic visit).  <u>After IPC removal</u> Follow-up for any issues after IPC removal.

\* Inflammatory markers include WCC and CRP.

\*\* Monthly follow-up if IPC is removed

## 8. Assessment of Safety

### 8.1 Summary of known and potential risks and benefits

Mupirocin is a topical antibiotic used worldwide for 25 years with a strong safety record. Applied topically, it has insignificant systemic absorption and, even if absorbed, is rapidly metabolised in the liver and renally excreted. It is also widely used as a prophylactic agent in peritoneal dialysis and is currently incorporated into the International Society for Peritoneal Dialysis (ISPD) guidelines for infection prevention. Whether this strategy applies to IPC infection is unknown. The results of this study will provide the answer to whether topical mupirocin prophylaxis reduces/prevents infection in patients fitted with an IPC for drainage of MPE.

Previously, we investigated the safety of topical mupirocin prophylaxis in 50 patients and all patients in the pilot study reported good tolerance. Concerns about long-term use of mupirocin may be raised. Mupirocin has been used for 25 years and resistance has not been an issue. MPE patients also have short lifespan (median <6 months) so the duration of use is limited. The burden associated with the research mainly relates to the inconvenience of follow-up phone calls/clinic visits. The outcomes of the study will guide clinical care in the future and allow us to optimise management of patients with malignant effusion, with the primary aim of improving quality of life measures and reducing the burden from hospitalisations.

Potential participants will be informed that not enrolling in the study will not put them at any disadvantage and they will receive standard care. Participation in the study will not be of direct benefit on an individual basis but rather provide the evidence base in which future patients will be able to have the best management and care of malignant pleural effusion.

### 8.2 The safety parameters and the methods / timing for assessing, recording, and analysing safety parameters

The procedure of applying topical mupirocin is easy and simple to follow. The participants will be monitored as per standard of care guidelines and during follow-ups throughout the study.

### 8.3 Data and Safety Monitoring Committee (DSMC)

The Data Safety Monitoring Committee's remit is to ensure the safety of study participants through study procedures, reviewing adverse events and serious adverse events and consider new data (recently published studies) that may determine the validity of study continuation. All deaths, anticipated or unanticipated will be discussed with the DSMC. The committee 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 TSC, who oversees the study and determines whether the study should continue, or be suspended or terminated.

### 8.4 Adverse Events (AE)

All adverse events relating to the study, serious and non-serious, will be fully documented on the appropriate CRFs. For each AE, the investigator will provide the onset and end dates, 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.

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 and 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 in individual participant AE logs. Events will also be reported if a causal link (relatedness) between the AE and the study is suspected but *not* confirmed.

## **Expected adverse events**

### Topical mupirocin prophylaxis arm

This is a simple intervention in addition to the usual standard care while carrying out dressing changes/drainages.

Potential Complications include:

1. Redness
2. Itchiness
3. Swelling
4. Skin irritation
5. Pain (around the exit-site and/or related to IPC)

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 an AE

- 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.

### **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
- 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.

### Causal Relationship (Relatedness)

Medical judgement 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 CRFs.

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

If an SAE is reported, the investigator must provide the causal relationship. The investigator has the obligation to report AEs during the specified time of the study.



The September 2016 NHMRC Position Statement on the Reporting of Adverse Events notes where it is appropriate to report events to their Ethics board at the time and where they should otherwise be noted in the Annual Report. All sites will have a responsibility to report SAEs to the lead site within 24hrs of local notification. If in doubt as to the classification, sites are encouraged to contact the lead site to discuss. The local Ethics board should be notified as per local guidelines.

### Adverse Events Logs

AE logs will be followed up until resolution. Where AEs are not resolved at study completion this will be noted on the AE log. This participant group is under the ongoing care of the respective respiratory physicians unrelated to the study and so adverse events will have ongoing management.

## 9. Data Management, Statistical Analysis and Record Keeping

### 9.1 Statistical Plan

Data will be analysed on an intention-to-treat basis and per protocol basis. The primary outcome will be analysed using chi-square test and subsequent logistic regression analyses allowing adjustments for minimisation variables. A secondary analysis of the primary outcome will utilize the time to event data, where cumulative incidence plots will be presented, and the log-rank statistic used to compare the treatment groups. In addition, Cox regression models will be used to calculate cause specific hazard ratios adjusted for minimisation variables. A competing risk analysis will also be performed to account for the competing risk of death in estimation of event rates. For binary or continuous secondary outcomes, inter-group differences will be examined using chi-square tests or two sample t-tests respectively, with additional logistic and linear regression analyses adjusting for minimisation variables. Adverse and serious adverse events will be reported in descriptive figures.

### 9.2 Sample Size

This study will enrol 419 patients to detect a difference in IPC-related infection rate between the treatment arms. The difference that we wish to detect is 10% in the Antibiotics Prophylaxis arm (i.e., a relative reduction in infection rates of 50%) vs 20% in the no antibiotics arm. The sample size calculation was carried out using an anticipated chi square test to compare these proportions, assuming a 5% significance level and a power of 80%. To achieve this, we would need 199 patients (with an additional 5% to allow for dropouts) per group, giving a total of 419 patients. The calculations were based on:

- IPC infections (pleural + tract + skin):

The pleural infection rate varied with clear dichotomy of UK/Australasian vs North American data. This is directly related to duration of catheter in situ, and affected by two key factors: In UK/Australasia i) significantly higher proportion of IPC patients have mesothelioma (and longer survival than those with metastatic carcinoma; hence longer catheter duration); ii) it is common practice to insert IPC early (as soon as MPE diagnosed) instead of using it as a last resort in the terminal phase. The TIME-2 (UK)<sup>9</sup> and AMPLE-2 (Australasia)<sup>15</sup> RCTs both registered a pleural infection rate of ~10%.

The tract infection and cellulitis rates are less well documented in the literature but (combined) are often similar to the pleural infection rates in published papers. Hence we estimated a 20% incidence for overall IPC-related infections.

- In the RCTs of topical antibiotics in PD patients, a two-third reduction in infection rates (vs control arms) were commonly reported.<sup>20-22</sup> We therefore estimated an incidence of 10% in

our treatment arm. Mahajan *et al*<sup>26</sup> found that mupirocin not only reduced the incidence of exit-site infection (ESI) and peritonitis caused by *S. aureus* (65% and 100% reduction respectively), but also led to a relative reduction of 60.5% and 55.0% for ESI and peritonitis respectively. A systemic analysis<sup>23</sup> of 14 studies found that mupirocin prophylaxis decreased the risk of *S. aureus* ESI by 72% [95%CI 60-81%] and peritonitis by 70% (52-81%) among PD patients. Mupirocin reduced the risks of ESI and peritonitis due to all organisms by 57% and 41% respectively.

- Drop-out: We have allowed a 5% drop-out rate, based on our AMPLE-1 trial<sup>12</sup> (4.8%; 7/146).

### 9.3 Interim analysis

The Trial Steering Committee plans two interim analyses to ensure continuation of the trial is practical and likely to produce meaningful results. This includes

1. an interim analysis after ~90 patients have been enrolled and completed follow-up. The purpose is to i) assess the rate of recruitment and determine the feasibility of fulfilling the enrolment target and ii) futility - observe the actual incidence of event rates in the control group to ensure the study is adequately powered to detect a clinically meaningful difference.
2. an interim analysis after ~200 patients have been enrolled and completed follow-up. The purpose will be to address both superiority and futility. The superiority stopping rule will follow an O'Brien-Flemming approach with an interim analysis significance threshold set at 0.005 and the final analysis significance level adjusted to account for this interim analysis, with significance level of 0.049.

In both analyses futility rules will be set to determine if the study should continue and if it is likely to produce a clinically meaningful difference given the initial results.

### 9.4 SAP deviations

SAP deviation(s) from the original plan will be initially reported to the TSC and described and justified in the protocol and/or in the final report, as appropriate.

### 9.5 The selection of participants to be included in the analyses

All evaluable participants will be included in the final analyses.

#### Time schedule of data collection:

##### Pre-Procedure:

**Baseline** data will be collected once informed consent has been obtained.

Data collected will include:

1. Demographics including age & sex.
2. ECOG status
3. Comorbidities
4. Malignancy data
5. Baseline bloods (WCC & CRP)
6. Baseline CXR findings (e.g., trapped lung)
7. Current antibiotic, immunosuppressant or cancer treatment
8. Pleural effusion data including laboratory results and previous interventions.

##### Post-Procedure:

Data regarding the procedure will be collected.

## **Topical Mupirocin ARM**

### **T0 / INDEX procedure:**

1. IPC insertion & inpatient drainage
2. Education on IPC home drainage and care
3. Education on the use of topical mupirocin

### **T1 (6-48 hrs post procedure):**

1. Evaluation of exit-site and application of topical mupirocin with dressing changes.

### **Before Discharge:**

1. IPC education

## **No Antibiotics (Standard Care) ARM**

### **T0 / INDEX procedure:**

1. IPC insertion & inpatient drainage
2. Education on IPC home drainage and care
3. Education on standard exit-site care

### **T1 (6-48 hrs post procedure):**

1. Evaluation of exit-site and standard care for dressing changes.

### **Before Discharge:**

1. IPC education

## **Follow-ups for both arms**

### **Weekly (or monthly after IPC removal) follow-up up to 6 months:**

1. Details on IPC drainage and dressing change
2. Details on mupirocin application (and reason for missed doses) for Topical Mupirocin arm
3. Adverse event review
4. Pleural fluid culture testing (if clinic visit)
5. IPC removal details

## **9.6 Data Management**

All procedures for the handling and analysis of data will be conducted using GCP ICH guidelines, the National Statement on Ethical Conduct in Human Research (2007) - *Updated May 2015* and local policies and procedures for the handling and analysis of data.

Patient privacy and confidentiality will be maintained, as any information that identifies participants will be available only at the enrolment study site and only to designated study investigators, all of whom will either have signed a confidentiality agreement or be employees of the hospital.

Data collected will be stored at site on password-protected computers accessible only by the site research staff and will be held in the department where the PI is based. All physical documentation will be stored in a secure, locked filing cabinet with restricted access in private offices within the PI's department in line with the Australian Code for the Responsible Conduct of Research for clinical trials and local policy guidelines for research data archiving. All data associated with this trial will be archived for 15 years after the completion of the project.

## 9.7 Plan for 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 of the required information is collected from the patient). We will attempt to minimise the missing data due to item non-response. Throughout the duration of the trial, participants will have regular contact with the respiratory department and the study team. 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 rate 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.

## 10. Monitoring / Audit

### 10.1 Monitoring permissions

The study investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but is not limited to, review by external sponsors, Human Research Ethics Committees and institutional Governance review bodies.

### 10.2 Monitoring procedure

This study will have site monitoring carried out by the lead site. Source data will be scrutinised to ensure the provision of robust data. Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. Any discrepancies should be resolved with the site PI or otherwise documented as File Notes. Procedure deviations and or violations may be determined at this time and will need to be reported according to local procedure/policy. Source documents are filed at the investigator's site.

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. Quality Control and Quality Assurance

### 11.1 Protocol compliance

The study will be conducted in compliance with the protocol, Good Clinical Practice, the National Statement and relevant local laws.

### 11.2 Quality Control

CRFs will be created and tested in conjunction with the study sites *before* study commencement to ensure the practicality and viability of full completion. All sites will be asked to promptly complete relevant CRFs and send through to the lead site. Where data points cannot be entered, the sites will be encouraged to contact the lead site to discuss. The lead site will review all CRFs as they are received for anomalies including missing data points to expedite data query resolution.

### Essential Documents

Investigator Site File (separate list for lead site Trial Master File)

- Pre-study opening

- PI + AI signed / dated Curriculum Vitae
- PI + AI current GCP certificate
- HREC study approval
- Governance study approval
- Signed CTRA
- Initial Contents
- Protocol/Amendment(s) and CRFs
- Blank Informed Consent Form
- Any other written information provided to subjects
- Regulatory Approvals/Notifications Where Required For Revision(s) of:
  - informed consent form
  - any other written information to be provided to the subject
  - any other documents given approval/favourable opinion
  - continuing review of trial (where required)
  - monitoring visit reports
  - relevant communications
  - completed filed forms etc
  - signed informed consent forms
  - source documents
  - signed, dated and completed
- Case Report Forms (CRF) Documentation of CRF Corrections/Revisions
- Notification by originating investigator to lead site of Serious Adverse Events and Related Reports
- Interim or Annual Reports to HREC
- Subject Screening and Enrolment Log
- Subject Identification Code List
- Subject Enrolment Log
- Delegation of Responsibilities Log
- Record of retained body fluids/ tissue Samples (if any)

## 12. Ethics

### 12.1 Ethics

The study will be carried out in full compliance with the study protocol, the principles laid down in the Declaration of Helsinki, as of October 1996 in accordance to the ICH Harmonised Tripartite Guideline for Good Clinical Practice (GCP), the National Statement on Ethical Conduct in Human Research (2007) - **Updated May 2015** and relevant SOPs.

The study will not be initiated before the clinical trial protocol and patient information and consent form have been reviewed and received approval from the Ethics Committee and other regulatory authorities (Research Governance) as required by local laws and regulations.

If a protocol amendment is needed, the changes will not be instituted until the amendment and revised PICF (where appropriate) have been reviewed and received approval from the relevant Ethics committee and other regulatory authorities as required by local laws and regulations. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately providing the regulatory authority and Ethics committee are notified as soon as possible and retrospective approval is requested. Protocol amendments exclusively for

logical and administrative changes may be implemented with notification only of the ethics board and other regulatory authorities as required by local laws and regulations.

## 13. Budget, Financing, Indemnity and Insurance

### 13.1 Finance agreements

Funding will be sought from grant funding bodies to cover staffing time for study administration. The relevant contracts will be signed as separate documents to the protocol. Other time is given in kind as approved by the relevant heads of department. Where grant funding does not cover all the costs, Prof Lee's funds at the Institute for Respiratory Health will cover any shortfalls. The costs for Mupirocin cream will also be absorbed by the Pleural Medicine Unit led by the CPI-Lee.

## 14. Registration / Publication

### 14.1 Publication policy

The study will be registered with the Australian New Zealand Clinical Trials Registry (ANZCTR). The study results will be disseminated through publication in an international journal.

## 15. References

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