Study protocol for a randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax

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ABSTRACT

Introduction: Current management of primary spontaneous pneumothorax (PSP) is variable, with little evidence from randomised controlled trials to guide treatment. Guidelines emphasise intervention in many patients, which involves chest drain insertion, hospital admission and occasionally surgery. However, there is evidence that conservative management may be effective and safe, and it may also reduce the risk of recurrence. Significant questions remain regarding the optimal initial approach to the management of PSP.

Methods and analysis: This multicentre, prospective, randomised, open label, parallel group, non-inferiority study will randomise 342 participants with a first large PSP to conservative or interventional management. To maintain allocation concealment, randomisation will be performed in real time by computer and stratified by study site. Conservative management will involve a period of observation prior to discharge, with intervention for worsening symptoms or physiological instability. Interventional treatment will involve insertion of a small bore drain. If drainage continues after 1 hour, the patient will be admitted. If drainage stops, the drain will be clamped for 4 hours. The patient will be discharged if the lung remains inflated. Otherwise, the patient will be admitted. The primary end point is the proportion of participants with complete lung re-expansion by 8 weeks. Secondary end points are as follows: days in hospital, persistent air leak, predefined complications and adverse events, time to resolution of symptoms, and pneumothorax recurrence during a follow-up period of at least 1 year. The study has 95% power to detect an absolute non-inferiority margin of 9%, assuming 99% successful expansion at 8 weeks in the invasive treatment arm. The primary analysis will be by intention to treat.

Ethics and dissemination: Local ethics approval has been obtained for all sites. Study findings will be disseminated by publication in a high-impact international journal and presentation at major international Emergency Medicine and Respiratory meetings.

Strengths and limitations of this study

- This will be the largest randomised trial of the management of large primary spontaneous pneumothorax (PSP) that includes long-term follow-up.
- The study includes an assessment of efficacy, safety, healthcare usage and patient-centred outcomes such as pain and return to work.
- The findings will provide high-level evidence for the optimum initial management of PSP and will be generalisable to clinical practice internationally.
- The nature of the treatments being compared means that blinding of participants to treatment allocation is not possible; however, the ability for patients to decline involvement combined with unbreakable allocation concealment means that participant and clinician bias towards one treatment modality or another is less likely to confound the study results.

INTRODUCTION

Primary spontaneous pneumothorax (PSP) is a significant global health problem affecting adolescents and young adults. The incidence of PSP is around 18–28/100 000 per year for men and 1.2–6/100 000 per year for women.1,2 It usually occurs in the absence of underlying lung disease or trauma; however, anatomical abnormalities such as subpleural blebs are present in up to 90% of cases.3,4 Tobacco smoking is a major risk factor, and otherwise healthy male smokers have a
The current management of PSP is variable, with sparse evidence from randomised controlled trials to guide treatment. Current guidelines from Britain and North America emphasise the importance of intervention in most patients. This may involve insertion of a chest drain, hospital admission and the need for thoracic surgery in some individuals. This invasive approach has recently been questioned.

Throughout the early 20th century, the treatment of PSP was predominantly conservative, with bed rest for most patients, and invasive treatment reserved for severely symptomatic episodes. In 1966, the first large series of patients with PSP who had conservative community management was published. Sixty-eight patients aged between 15 and 44 years with large and small PSPs were discharged and managed in the community without intervention. Re-expansion was observed in 78% by 4 weeks and in 97% by 8 weeks. Although not a randomised controlled trial, this case series suggested that discharging patients without intervention was safe and effective. A conservative initial approach to PSP has since been suggested by others. Despite this, rates of intervention in PSP have steadily increased over subsequent decades. The reasons that an interventional approach has become standard practice are unclear. It may relate to the increasing ease of tube insertion, better tube design and also physicians perceiving a need to actively evacuate the air. In addition, there is a perception that PSP is potentially serious because of the theoretical risk of tension pneumothorax. Hence, intervention may be considered a safer approach. However, case series do not support the assertion that conservative treatment is less safe.

Interestingly, the rate of pneumothorax recurrence among patients managed conservatively in the 1966 study was only 6% after 2 years and 11% after 4 years, strikingly lower than more recent data from invasively managed patients. In the last 10–15 years, prospective studies of patients with PSP undergoing procedures report cumulative 1-year recurrence rates of 23–27%. One possible mechanism for a lower recurrence rate with conservative management is that healing of the pleural defect may be facilitated by allowing the lung to stay collapsed initially followed by slow re-expansion.

Although PSP may be associated with pain and shortness of breath, the symptoms are variable and improve quickly. Patients are often asymptomatic after 24–48 hours, and 46% of them wait more than 2 days before presenting for medical assessment.

There are a number of issues regarding the current established practice of intervention in PSP. From a patient perspective, the insertion of a chest drain is a painful procedure; in one study, 50% of patients experienced pain levels of 9–10 on a scale of 10. Chest drain insertion has a number of important complications such as injury to organs, bleeding and infection. Concern about these complications remains, even with the use of modern small bore chest drains. The management of an underwater seal drain requires hospital admission, and hence time off work or away from other duties, with an average length of stay of around 4 days. If the air leak continues beyond 3–5 days, patients often proceed to surgery, with its attendant costs and potential harms.

In summary, significant questions remain regarding the optimal initial approach to the management of large PSP. In the absence of a well-conducted, randomised, controlled trial, it is unlikely that clinicians will change current practice which has been entrenched for decades and is re-enforced by current international guidelines. If completed, this study will be the largest international trial in PSP ever undertaken and will be the first to address the fundamental management question of conservative versus invasive management of PSP.

**Aims and hypotheses**

Our main aim is to determine whether conservative management of large PSP is an effective and acceptable therapeutic option. Our hypotheses are as follows:

- The resolution of large PSP will be similar after 8 weeks with either therapeutic regimen.
- Conservative management will be associated with shorter times to recovery due to a reduced risk of persistent air leak, higher levels of patient satisfaction and reduced intervention-related morbidity.
- Conservative management lowers the risk of PSP recurrence due to improved healing of the lung defect.

**METHODS AND ANALYSIS**

**Study design**

This is a multicentre, prospective, randomised, controlled, open label parallel group, non-inferiority study of conservative versus invasive treatment of PSP. It will involve the randomisation of 342 participants presenting to an Emergency Department (ED) in Australia and New Zealand with a PSP.

**Screening and selection**

After the radiological diagnosis of PSP has been confirmed, and eligibility assessed, potential participants will be approached by ED or Respiratory Medicine clinicians about the possibility of taking part in the study. The doctor will give an initial overview of the study and then provide the study participant information and consent form (PICF) to read. Time will be allowed for the participant to ask questions about the study. Study enrolment will only occur following the completion of the informed consent process. Potential participants will be made aware that their clinical management will not be affected by their decision to either take part or decline study participation, and that they can withdraw at any time. All sites will maintain screening logs of potentially
suitable cases of pneumothorax that were not enrolled noting the reasons for exclusion.

**Inclusion criteria**

PSP that is 32% or larger by the method of Collins,\(^3\) that is a ‘sum of interpleural distances’ \((A+B+C)\) of 6 cm or greater.

**Exclusion criteria**

▸ Previous spontaneous pneumothorax on the same side;
▸ Secondary pneumothorax, defined as pneumothorax occurring in the setting of acute trauma (including iatrogenic) or underlying lung disease including but not limited to COPD, pulmonary fibrosis, TB, cystic fibrosis, lung cancer and asthma that requires regular preventative medication or has been symptomatic (eg, nocturnal symptoms) within the past 2 years;
▸ Coexistent haemothorax;
▸ Bilateral pneumothorax;
▸ Physiological instability suggesting tension pneumothorax: systolic BP (SBP) <90 mm Hg, mean arterial pressure <65 mm Hg or HR ≥ SBP (ie, shock index HR/SBP ≥1);
▸ Age <14 years;
▸ Age >50 years (due to a higher incidence of underlying lung disease, ie, secondary pneumothorax);
▸ Pregnancy at the time of enrolment. All women of reproductive age will have a pregnancy test;
▸ Circumstances whereby the patient either does not have adequate support after discharge to re-attend hospital if required, or is unlikely to present for study follow-up;
▸ Air travel within the next 12 weeks if this cannot be deferred should the pneumothorax be slow to resolve.

**Randomisation**

Participants who fulfil the eligibility criteria and give informed consent will be randomised 1:1 to receive either conservative or invasive management. To maintain allocation concealment, participants will be randomised in real time, stratified by study site, using an adaptive biased coin (Urn) technique to maintain balance allocation at each site.\(^3\) The University of Western Australia will host the web-based randomisation system (Filemaker Server Advanced, Filemaker, Santa Clara, California, USA).

Owing to the nature of the interventions, it will not be possible to blind participants or investigators to treatment allocation. However, all study chest x-rays (CXR) which determine the primary outcome measure will be read by a radiologist blinded to all participant details.

**Initial clinical care**

The initial management received by participants prior to their randomisation will be as follows:

1. Oxygen as required (if \(\text{SpO}_2 < 92\% \) on room air).
2. Initial analgesia if required:
   ▶ Mild–moderate pain: paracetamol 1 g, plus a non-steroidal anti-inflammatory drug (NSAID), for example, ibuprofen 400–800 mg, if there are no contraindications to NSAID.
   ▶ Severe pain: paracetamol and an NSAID as for mild–moderate pain plus intravenous morphine with an initial bolus of 0.1 mg/kg (5–10 mg) with further doses titrated to effect, followed by one dose of oral narcotic (eg, oxycodone 5 mg orally).

**Conservative treatment protocol**

1. Participants will be observed for 4 hours and then a repeat CXR performed prior to discharge from the ED (figure 1).
2. Prior to discharge, participants must be able to walk comfortably around the ED to ensure that they are capable of undertaking routine activities of daily living.
3. Participants will switch to the invasive protocol if
   A. Significant symptoms persist despite adequate analgesia: chest pain and/or dyspnoea that is likely to prevent routine activities of daily living or such that the participant is unwilling to continue conservative treatment.
   B. Physiological instability develops during the observation period: SBP <90 mm Hg, HR ≥ SBP, respiratory rate (RR) >30/min, and \(\text{SpO}_2 < 90\% \) on room air.
   C. The repeat CXR shows that the pneumothorax is increasing in size, and there has been a trend in observations to suggest the development of tension. NB an increase in pneumothorax size on CXR alone does not necessarily require intervention if the participant’s clinical condition has improved or has remained stable.
4. Participants will be prescribed discharge analgesia according to their requirements while in ED: paracetamol, ± NSAID ± a short supply of oral narcotic.
5. Written discharge instructions will be provided; these include what to do in the event of deterioration and advice not to scuba dive or fly.
6. At any stage during follow-up if the participant has significant symptoms (as defined above), the investigator may elect to switch them to the interventional protocol.

**INTERVENTIONAL TREATMENT PROTOCOL**

1. A small bore \((<12 \text{ F})\) Seldinger-style chest drain will be inserted in either the second intercostal space mid-clavicular line anteriorly or the safety triangle laterally. The drain will be attached to an underwater seal. Suction will not be applied (figure 1).
2. A repeat CXR will be performed 1 hour after drain insertion. If the lung has re-expanded (pneumothorax now small with a sum of interpleural distances <6 cm), and there has been a reduction in symptoms if present initially, and the underwater drain is no
longer bubbling, the drain will be closed using a three-way tap and the patient observed for 4 hours. After 4 hours, if the pneumothorax size is stable on repeat CXR, and the participant remains clinically stable, the drain will be removed. Simple analgesia will be prescribed for residual symptoms, written discharge instructions provided and the participant discharged.

3. If initial drain insertion does not result in pneumothorax resolution, or the pneumothorax recurs under observation.

Figure 1 Flow diagrams for conservative and interventional treatment protocols.
A. The three-way tap will be opened and underwater seal drainage will restart.

B. Participants will be admitted under an appropriate inpatient team according to local protocols (General Medicine, Cardiothoracic Surgery or Respiratory Medicine). Subsequent interventions (additional drains, suction and requirement for surgery) will be at the discretion of the treating inpatient team.

C. Prior to discharge, a CXR will be performed after removal of all chest drains.

Follow-up assessments

Initial follow-ups at 24–72 hours, 2 weeks, 4 weeks and 8 weeks will be carried out face to face wherever possible, but can be carried out over the telephone if necessary with the investigator making arrangements with the patient to have CXR and spirometry performed. The reasons for missing or incomplete data will be noted. All participants will have the following assessments:

- Clinical review and datasheet completion at 24–72 hours, 2 weeks, 4 weeks and 8 weeks after enrolment. If the participant cannot attend the scheduled clinical review, completion of the follow-up questionnaire will be carried out over the telephone.
- A CXR will be undertaken at 2, 4 and 8 weeks until pneumothorax resolution.
- Spirometry (FEV1, FVC, height and weight) will be performed after pneumothorax resolution.
- Participants will be telephoned at 6 and 12 months post-enrolment and then yearly for up to 5 years. Pneumothorax recurrence and other follow-up data will be collected, including study-related adverse events (AE). In addition, a search of Clinical Information Systems, and admission and ED attendance records, will be undertaken at these time points.

Study measurements

- Age, sex and smoking history.
- Date and time of symptom onset, presentation to ED, randomisation and discharge.
- Pneumothorax size using the method described by Collins et al25 for each study CXR. A single reporting radiologist will perform a blinded interpretation centrally, on large batches of de-identified CXRs presented in random sequence without date or time stamps to minimise any association between intervention and final outcome.
- Chest pain (verbal analogue) and dyspnoea (Borg scale) scores will be recorded at each study contact.
- Times of last chest pain, dyspnoea and use of analgesia will be recorded at each study contact.
- All procedures, including the date and time, will be recorded.
- Predefined complications and AE will be recorded:
  1. Tension pneumothorax;
  2. Haemothorax;
  3. Trauma to the heart, liver, spleen or bowel;
  4. Foreign body in chest wall;
  5. Foreign body in chest cavity;
  6. Infection of the skin and subcutaneous tissues requiring treatment with antibiotics;
  7. Infection of the pleural space (empyema) requiring treatment with antibiotics;
  8. Pneumonia requiring treatment with antibiotics;
  9. Sepsis, defined as likely infection and at least two of the following: temperature >38°C or <36°C, HR >90 bpm, RR >20/min, white cell count (WCC) >12 or <4×109/L;
- Other complications;
- Numbers of CXRs and chest CTs performed;
- Details of unplanned attendances relating to pneumothorax until 8 weeks after enrolment;
- Patient satisfaction at 8 weeks;
- Days of work or study lost by 8 weeks;
- Pneumothorax recurrence. Defined as a pneumothorax on the same side on a CXR performed after pneumothorax until 8 weeks after enrolment; an air leak (ie, ongoing leak) rather than a recurrence.

Primary outcome

The proportion of participants with complete lung re-expansion by 8 weeks.

Secondary outcomes

- Persistent air leak, defined by the presence of a chest drain for 5 days or longer,
- Pneumothorax recurrence,
- Time to symptomatic recovery defined as: discharge from hospital and resolution of symptoms and cessation of analgesic medication,
- Complications and AE as defined above,
- Hospital bed days,
- Number of procedures and investigations,
- Days off work,
- Patient satisfaction at 8 weeks.

Data collection, storage and verification

Data will be recorded in paper case report forms at the time of each patient contact. These will be faxed to the study lead site for checking followed by entry into the secure study database. Original datasheets will be securely stored at each site according to local ethics protocols. Research staff from the lead site will perform site visits and source data verification.

Statistical analysis

The primary outcome of lung re-expansion by 8 weeks will be analysed using a non-inferiority approach (ie, one-tailed α=0.05). Logistic regression will determine the effects of the randomised treatment, conservative versus intervention.
As a secondary analysis, the potential confounding and interaction effects of age, smoking status and initial pneumothorax size on dichotomous outcomes will be examined. Site will be included in the primary analysis as a categorical variable. Cox proportional hazards regression will be used to analyse time interval outcomes (recovery and pneumothorax recurrence). The primary analysis will be by intention to treat (ITT). Patients initially allocated to conservative treatment that switch to invasive treatment will remain in their original group for the purpose of ITT. Per-protocol analyses will also be performed.

**POWER CALCULATION**

A sample size of 274 has the ability to detect an absolute non-inferiority margin of 9%, assuming 99% successful expansion by 8 weeks in the invasive intervention group with a one-tailed $\alpha$ of 5% and a power of 95%. This represents a 90% successful expansion rate with conservative treatment, that is, a failure rate of $\sim 10$. In other words, we wish to rule out a re-expansion rate of <90% after 8 weeks with 95% power. The relatively high power has been chosen in order to minimise the chance of failing to confirm our hypotheses of non-inferiority with a clinically relevant margin, for a treatment that may be highly desirable to patients. High study power is recommended for non-inferiority studies. Allowing for a dropout rate of up to 20%, we plan to recruit 342 participants. However, this number may be adjusted according to the actual number of dropouts observed.

**Ethics approvals, data and safety monitoring**

Local ethics approval has been obtained for all recruiting sites. Written informed consent will be obtained before any study activity or intervention according to International Conference on Harmonisation (IHC) Good Clinical Practice (GCP), and regulatory and legal requirements. Each signature will be personally dated by each signatory or the participant’s legally accepted representative. The consent form and all study case report forms will be securely retained by the investigator as part of the study records. All participants or the participant’s legally accepted representative will receive a copy of the signed consent form.

All participants will be informed that their personal study-related data will be used by the principal investigator in accordance with the local data protection law. All participants will be informed that their medical records may be examined by authorised monitors or clinical auditors appointed by appropriate ethics committee members and by inspectors from regulatory authorities.

Data will be collected at each trial visit regarding any AE and serious AE as defined by the IHC GCP guidelines. All serious AE causally related to treatment procedures will be reported to the relevant ethics committees, the lead site and the independent Data and Safety Monitoring Committee (DSMC) for their review and recommendations. The DSMC comprises independent clinicians with an interest in pneumothorax and a statistician. Overview is carried out through the review of AE and serious AE, all of which are reported at the regular committee meetings. Each meeting determines the Board’s recommendation to the Steering Committee as to whether the study is safe to continue.

The trial is registered with the Australia New Zealand Clinical Trials Registry—ACTRN1261100184976.

**Dissemination**

Study findings will be disseminated by publication in an international journal and presentations at international Emergency Medicine and Respiratory Medicine meetings.

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**Contributors** GS and QAS conceived the idea for the study. ELB, SGAB and KP formed the working group that wrote the study protocol. The Steering Committee assisted with protocol design and study logistics, and
reviewed and took final responsibility for all study procedures. Site investigators (listed below) reviewed and commented on study procedures and documentation prior to study implementation. ELB and SGAB piloted the study protocol at Royal Perth Hospital prior to full implementation. Site investigators—Australia: Armadale-Kelmscott Memorial Hospital, WA (Stephen P Macdonald); Blacktown and Mount Druitt Hospitals, NSW (James Kwan); Box Hill Hospital, VIC (Paul Buntine); Bundaberg Base Hospital, QLD (Michael Chang); Busselton Hospital, WA (Hugh M Mittenko); Calms Base Hospital, QLD (Graham Simpson); Casey Hospital, VIC (Alastair Meyer); Dandenong Hospital, VIC (Kirsty Povey); Fremantle Hospital, WA (Yusuf Nagare); Fiona Stanley Hospital, WA (Yusuf Nagree); Gold Coast Health Service District (Gold Coast University Hospital, and Robina Hospital) (Gerben Keijzers); Ipswich Hospital, QLD (Kylie Baker); John Hunter Hospital, NSW (Conrad Loten); Mater Hospital, QLD (Joseph Y Ting); Monash Medical Centre, VIC (Diana Egerston-Warburton); Nambour General Hospital, QLD (Ogilvie N Thom); Rockingham General Hospital, WA (Rod Ellis); Royal Brisbane and Women’s Hospital, QLD (Kevin Chu); Royal North Shore, NSW (Mark Gillett); Royal Perth Hospital, WA (Daniel M Fatovich); Sir Charles Gairdner Hospital, WA (David Mountain); St George Hospital, NSW (Stephen E Asha); Swan District Hospital, WA (Susan Mills); The Prince Charles Hospital, QLD (Frances Kinner); The Sutherland Hospital, NSW (Allison M Moore); Toowoomba Hospital, QLD (Simon Tebbutt); Townsville General Hospital, QLD (Jeremy Furry); New Zealand: Auckland City Hospital (Margaret Wilsher), Christchurch Hospital (Lutz Becker), Middlemore Hospital (Hamish Read), Waikato Hospital (Robert J Hancox), Wellington Hospital (Kyle Perrin).

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Competing interests
None declared.

Patient consent
Obtained.

Ethics approval
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REFERENCES
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