Statistical analysis plan for the PSP trial: a randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax

Abstract

Background: The randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax (PSP) study is an international, multicentre, randomised, open-label, non-inferiority study to evaluate whether conservative management of PSP is an acceptable therapeutic option. The nature of the treatments means that blinding of participants to treatment allocation is not possible.

Objective: To minimise bias by defining our analysis approach prior to completing the study and looking at the trial data.

Methods: Taking into consideration the aspects of trial design and reporting specific to non-pharmacological interventions, we developed a statistical analysis plan (SAP) for reporting and analysing the trial including our approach to expected protocol deviations, withdrawals, missing data and loss to follow-up.

Results: The data fields described are those outlined in the study protocol published previously. We describe the plan for the presentation and comparison of baseline characteristics, participant flow, interventions, process measures and trial outcomes. The primary outcome will be analysed by intention-to-treat with an equivalence (non-inferiority) approach, and a sensitivity analysis will assess how potential confounding factors influence the assessment of treatment effect. Secondary outcomes will be analysed using traditional (two-sided) statistical methods.

Conclusion: A SAP for the PSP study has been defined and is available in the public domain prior to the completion of recruitment, thus minimising the risk of analytic bias.

Trial registration: Australia New Zealand Clinical Trials Registry-ACTRN12611000184976.
Introduction

The PSP study is a randomised controlled trial of invasive versus conservative management of primary spontaneous pneumothorax (PSP). The aim of this multi-centre, randomised, open-label, non-inferiority study is to evaluate whether conservative management is an acceptable therapeutic option compared to invasive management, such as pneumothorax drainage by insertion of a chest drain.

The nature of the treatment arms being compared means that blinding of participants to treatment allocation is not possible. This may lead to bias with respect to outcome reporting. It is possible that study participants will not be typical of all patients with a PSP because clinicians may have a preference for intervention based on PSP characteristics in any individual participant and because of local study site preferences/policy. However, the study design includes robust allocation concealment as part of randomisation following the informed consent process so that participant and clinician bias towards a treatment modality is less likely to confound the study results.

The purpose of making the statistical analysis plan (SAP) available in the public domain before completion of recruitment is to minimise the risk of analytic bias.

The aims, hypotheses and design of this study have been described in detail previously. A summary of trial design relevant to the SAP will be presented, however this article will focus on the analysis and presentation of data.

Study design overview

This trial is a prospective, multicentre, parallel-group, randomised, non-inferiority study of conservative treatment in patients with a primary spontaneous pneumothorax. The primary outcome variable is “the proportion of participants with complete lung re-expansion by 8 weeks”. The trial was prospectively registered (ACTRN12611000184976) and the study protocol has been previously published [Brown SG et al BMJ Open 2016; 6; e011826.], details of exclusion criteria and study treatments can be found there.

Aims and hypotheses

The main aim is to determine whether conservative management of large primary spontaneous pneumothorax (PSP) is safe and effective and therefore an acceptable therapeutic option. The particular hypotheses tested are that:

- The proportion with resolution of large PSP after 8 weeks will not be worse for conservative compared to invasive management (the primary outcome analysis).
- Conservative management will be associated with shorter times to functional recovery due to a reduced risk of persistent air leak, greater 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.

Definitions of outcome variables

Primary outcome variable:
The primary outcome variable is complete lung re-expansion by 8 weeks. Complete lung re-expansion is defined by the local study investigator indicating that radiological expansion has occurred at a study follow up visit.
Participants in whom the 8 week clinic visit occurred after 56 days are treated as ‘missing’ rather than imputed as ‘failure’, unless a later CXR demonstrates a persisting pneumothorax, thereby confirming treatment failure. The ‘window’ for an 8-week visit outcome will be the week up until 56 days; thus any demonstrated resolution prior to 56 days is taken as a primary outcome of resolution, any persistent pneumothorax after 49 days (including after 56 days) is taken as a primary outcome of failure, and remaining cases are treated as missing data.

Two post-hoc sensitivity analyses will be undertaken:

i) Primary: Extension of the 8-week clinic visit definition to 63 days (week 8 plus 1 week), thus increasing the acceptable window for an 8-week visit from between 49 and 63 days; thus any demonstrated resolution prior to 63 days is taken as a primary outcome of resolution, any persistent pneumothorax after 49 days (including after 63 days) is taken as a primary outcome of failure, and remaining cases are treated as missing data. A frequency plot of the days after randomisation that the 8 week visit occurred will be presented.

ii) Secondary: Complete lung re-expansion by 56 days (week 8) in which there is evidence of radiological resolution with all resolutions after 56 days imputed as ‘failure’

These analyses would be by ITT with associated hypothesis tests in relation to the non-inferiority boundary of 9%.

Secondary outcome variables:

1. Radiological:
   i) Complete lung re-expansion by 8 weeks, assessed by independent study radiologists masked as to treatment allocation.
   ii) Chest xray size of the persisting pneumothorax, (up to 8 weeks), as assessed by the independent radiologist masked to treatment allocation.

The pre-specified analysis of the subgroup of participants in whom the resolution CXR was reported by both the clinician investigator and the blinded radiologist will be undertaken for complete radiological resolution of the primary spontaneous pneumothorax as determined by i) the treating physician and ii) the blinded radiologist in all participants with complete 8 week follow-up data at 56 days; (data after 56 days is treated as ‘missing’ rather than imputed as ‘failure’, unless a later CXR demonstrates a persisting pneumothorax, thereby confirming treatment failure).

These analyses would be by ITT with associated hypothesis tests in relation to the non-inferiority boundary of 9%.

2. Investigations:
   i) Number of patients who had at least one radiological assessment by CT scan of the chest within the 8 week study period.
   ii) Number of CT scans undertaken in each patient group.
   iii) Number of CXRs undertaken in each group.
3. Interventions:
   i) Number of patients who had at least one invasive procedure: needle aspiration, chest drain insertion, application of suction, pleurodesis, and/or any surgical procedure
   ii) Total number of invasive procedures: needle aspiration, chest drain insertion, application of suction, pleurodesis, and/or any surgical procedure.
   iii) For those patients requiring a chest drain, the number requiring chest tube drainage for 72 hrs or longer (persistent air leak).
   iv) Hospital bed days defined as the total number of days in hospital from the time of randomisation to final study visit at 8 weeks.

4. Complications:
   i) The number of complications of allocated treatment: Tension pneumothorax, haemothorax, trauma (to heart, liver, spleen or bowel), foreign body in chest wall or chest cavity, infection of the skin and subcutaneous tissues requiring antibiotics, infection of the pleural space (empyema), pneumonia requiring antibiotics, sepsis (defined as likely infection and at least two of: temperature >38 or <36 degrees, HR >90 beats/min, RR >20/min, WCC>12 or <4 x 109/L).

5. Clinical / patient reported outcomes:
   i) The number of patients who reported complete symptomatic recovery within the 8 week period; recovery defined as discharge from hospital and resolution of symptoms (pain and dyspnoea score of 0) and cessation of analgesic medication.
   ii) Time to symptomatic recovery, defined as number of days (up to 8 weeks) following randomisation until the following criteria are met: discharge from hospital and resolution of symptoms (pain and dyspnoea score of 0) and cessation of analgesic medication.
   iii) Days off work, defined as number of days from the time of randomisation to the completion of the study period that the participant reported lost from work, study, or looking after children because of the pneumothorax.
   iv) Patient satisfaction at each study follow up visit, defined as the participant questionnaire satisfaction score at each study visit (very dissatisfied, dissatisfied, slightly dissatisfied, slightly satisfied, satisfied, or very satisfied).

6. Pneumothorax Recurrence
   i) The number of patients with pneumothorax recurrence, defined as a second primary spontaneous pneumothorax occurring at any time from resolution of the index event to 12 months post randomisation, on the same side as the index event. This includes recurrent episodes derived from review of hospital records or self-reported by participants.
   ii) Time to first recurrence.
   iii) Number of participants who had a contralateral PSP, and total number of contralateral PSPs.

Analysis principles

- Analyses will be by intention-to-treat and per-protocol. Patients initially allocated to conservative treatment that receive invasive treatment will remain in the conservative
group, as the option of invasive treatment is available in the conservative treatment algorithm.

- Analyses for the primary outcome variable will be unadjusted.
- Some important participant characteristics will be the subject of possible subgroup analysis (described below). Whether or not the characteristics are associated with a different treatment outcome will be tested by an interaction term between the characteristic and the treatment.

**Justification of the sample size**

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 power of 95%. This represents a 90% successful expansion rate with conservative treatment, i.e. a failure rate of ~1 in 10. In other words we wish to rule out a re-expansion rate of less than 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.

**Interim analyses**

No interim analyses are planned in this study.

**Statistical analysis**

**Trial profile**

The flow of patients through the study will be presented in a Consolidated Standards of Reporting Trials (CONSORT) diagram (Figure 1).

**Characteristics of patients and baseline comparisons**

Baseline characteristics will be presented by treatment group. Discrete variables will be presented as numbers and percentages (calculated using the number of patients for whom data are available). When values are missing, the denominator will be stated. Continuous variables will be summarised as a mean (with SD), and a minimum, maximum and median (with interquartile range) will be provided for each variable in a supplementary appendix. The following baseline characteristics will be presented:

- Age
- Sex
- Smokers (current/past)
- Body mass index
- Time from symptom onset to presentation
- Analgesia prior to ED
- Chest pain score at randomisation
- Dyspnoea score at randomisation
- Pneumothorax size at randomisation (cm)

**Description of analyses**

The table shows the analyses in relation to the particular variables:
<table>
<thead>
<tr>
<th>Variable</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete lung expansion after 8 weeks: researcher defined</td>
<td>Absolute risk difference with 95% CI and a Chi-square testing whether the point estimate is less than the lower confidence bound</td>
</tr>
<tr>
<td>Complete lung expansion after 8 weeks: masked investigator defined</td>
<td>Absolute risk difference with 95% CI and a Chi-square testing whether the point estimate is less than the lower confidence bound</td>
</tr>
<tr>
<td>Size of persisting pneumothorax</td>
<td>T-test if normality assumptions are met. Alternatively Mann-Whitney U with Hodges-Lehmann estimator of location difference with 95% CI</td>
</tr>
<tr>
<td>At least one CT chest scan</td>
<td>Absolute risk difference with 95% CI and express as relative risk with 95% CI</td>
</tr>
<tr>
<td>Number of CT chest scans</td>
<td>Poisson regression to give relative rate and 95% CI</td>
</tr>
<tr>
<td>Number of CXR</td>
<td>Poisson regression to give relative rate and 95% CI</td>
</tr>
<tr>
<td>At least one invasive procedure</td>
<td>Absolute risk difference with 95% CI and express as relative risk with 95% CI</td>
</tr>
<tr>
<td>Number of invasive procedures</td>
<td>Poisson regression to give relative rate and 95% CI</td>
</tr>
<tr>
<td>Required a chest drain for 72 hours or more</td>
<td>Absolute risk difference with 95% CI and express as relative risk with 95% CI</td>
</tr>
<tr>
<td>Hospital bed days</td>
<td>T-test if normality assumptions are reasonable although past experience is that a, logarithm transformation is often needed for time variables where the exponent of the difference in logarithms can be interpreted as the ratio of geometric mean. Alternatively Mann-Whitney U with Hodges-Lehmann estimator of location difference with 95% CI</td>
</tr>
<tr>
<td>Complications</td>
<td>Each would be described as an absolute risk difference with 95% CI also expressed as a relative risk with 95% CI</td>
</tr>
<tr>
<td>Number with complete symptomatic recovery</td>
<td>Absolute risk difference with 95% CI and as relative risk with 95% CI</td>
</tr>
<tr>
<td>Time to symptomatic recovery</td>
<td>Kaplan-Meier curves for illustration and estimation of quantiles; Cox PH for estimation of HR</td>
</tr>
<tr>
<td>Time off work</td>
<td>T-test if normality assumptions are reasonable although past experience is that a logarithm transformation is often needed for time variables where the exponent of the difference in logarithms can be interpreted as the ratio of geometric mean.</td>
</tr>
<tr>
<td>Outcome</td>
<td>Statistical Test</td>
</tr>
<tr>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Alternatively Mann-Whitney U with Hodges-Lehmann estimator of location difference with 95% CI</td>
<td></td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td>Ordinal regression to estimate the Odds Ratio with 95% CI for a better versus worse response</td>
</tr>
<tr>
<td>At least one Pneumothorax recurrence</td>
<td>Absolute risk difference with 95% CI and also expressed as relative risk with 95% CI</td>
</tr>
<tr>
<td>Time to pneumothorax recurrence</td>
<td>Kaplan-Meier curves for illustration and estimation of quantiles; Cox PH for estimation of HR</td>
</tr>
<tr>
<td>At least one contralateral PSP</td>
<td>Absolute risk difference with 95% CI and also expressed as relative risk with 95% CI</td>
</tr>
<tr>
<td>Number of contralateral PSPs</td>
<td>Poisson regression to give relative rate and 95% CI</td>
</tr>
</tbody>
</table>

The potential confounding and interaction effects of age, smoking status, and initial pneumothorax size on dichotomous outcomes will be examined. A treatment interaction will be undertaken to examine whether treatment effect differed by site, by treating site as a fixed effect categorical variable.

**Subgroups**

A subgroup analysis will be undertaken in the conservative group to investigate whether there are any specific characteristics that are associated with i) failure to resolve at 8 weeks ii) receiving invasive intervention. Confounding variables include initial pneumothorax size, age, smoking, pain or breathlessness on presentation. For each randomised group, a subgroup analysis will be undertaken to investigate whether there are any specific characteristics that are associated with recurrence. Confounding variables include specific invasive procedures, size of initial pneumothorax, age and smoking.

**Conclusion**

We propose that this pre-specified SAP accords with high quality standards of internal validity and should minimise future analysis bias.
Figure 1. Flow of participants through the trial

Assessed for eligibility (n= )

Excluded (n= )
- Met an exclusion criteria (n= )
- Declined to consent (n= )
- Other reasons (n= )

Randomized (n= )

Allocated to conservative arm (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (give reasons) (n= )

Allocated to intervention arm (n= )
- Received allocated intervention (n= )
- Did not receive allocated intervention (give reasons) (n= )

FOLLOW-UP
- Lost to follow-up (give reasons) (n= )
- Discontinued intervention (give reasons) (n= )

ANALYSIS
- Excluded from analysis (give reasons) (n= )