A randomised controlled trial of conservative versus interventional treatment of primary spontaneous pneumothorax

INTRODUCTION

Primary spontaneous pneumothorax (PSP) is a significant global health problem affecting adolescents and young adults. Current management is variable, with sparse evidence from randomised controlled trials to guide treatment. Current guidelines emphasise the importance of intervention in most patients, which involves insertion of a chest drain, hospital admission, and thoracic surgery in some. This approach has recently been questioned and there is evidence to suggest that conservative management without intervention is effective and safe. The risk of recurrence may also be lower with conservative treatment because of better healing of the lung defect during slow re-expansion of the lung.

We propose to address the fundamental management question of conservative versus invasive management in a multicentre randomised controlled trial that will be the largest study of PSP ever undertaken. It has the potential to reduce morbidity and deliver economic benefits through reductions in procedures, complications and hospital admissions.

AIMS AND HYPOTHESES

Our aim is to determine whether conservative management of primary spontaneous pneumothorax is an acceptable therapeutic option.

Our specific hypotheses are that by 8 weeks the resolution of uncomplicated large PSP will be equivalent between approaches and that there will be additional benefits for conservative treatment, namely shorter times to recovery due to a reduced risk of persistent air leak, higher levels of patient satisfaction, and a reduced risk of PSP recurrence due to improved healing of the lung defect.

Data will also be collected to estimate direct and indirect costs for each therapeutic option; however a formal cost-benefit analysis will not be performed.

BACKGROUND

Primary spontaneous pneumothorax (PSP), a collapsed lung with air in the pleural cavity, 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. It usually occurs in the absence of underlying lung disease or trauma; however anatomical abnormalities such as sub-pleural blebs are present in up to 90% of cases. Tobacco smoking is a major risk factor and otherwise healthy male smokers have a 9- to 22-fold greater relative risk of developing PSP compared with non-smokers. Smoking is also associated with a higher recurrence rate.

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 both large and small PSP were discharged and managed in the community without intervention. Re-expansion was observed in
78% by four weeks and in 97% by eight weeks. Although not a randomised controlled trial, this case series suggested that discharging patients without intervention was safe and effective and a conservative approach to PSP has since been advocated by others.\textsuperscript{5,23} Despite this, rates of intervention in PSP have steadily increased over subsequent decades. The reasons that an interventional approach became 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. There is a perception that PSP is potentially serious, because of a risk of tension pneumothorax; hence intervention may be thought to be safer. Prospective case series do not support this assertion however, and conservative treatment appears to be safe.\textsuperscript{6,23}

Interestingly, the rate of pneumothorax recurrence among patients managed conservatively in the 1966 study was only 6% after two years and 11% after four 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 to drain the pneumothorax report cumulative one year recurrence rates of 23-27%\textsuperscript{7-10}, significantly higher than older case series of conservative management. One possible mechanism for a lower recurrence rate with conservative management is that by allowing the lung to stay collapsed initially, followed by slow re-expansion, healing of the pleural defect may be facilitated.

Although PSP may be associated with pain and shortness of breath, the symptoms are variable and improve quickly. Patients are often asymptomatic after 24 to 48 hours\textsuperscript{6,10,24-26} and many delay seeking medical attention initially (46% wait more than 2 days) because symptoms are mild.\textsuperscript{27}

There are a number of concerns 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.\textsuperscript{28} 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.\textsuperscript{29} The management of a chest drain and underwater seal requires hospital admission, and hence time off work or away from other duties, with an average length of stay of around 4 days.\textsuperscript{7,30} If the air leak continues beyond 3-5 days patients often proceed to surgery,\textsuperscript{3} with its attendant costs and risks.

In summary, significant questions remain regarding the optimal initial approach to the management of PSP. In the absence of a well designed and 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.

**RESEARCH PLAN**

This is a multicentre, prospective, randomised, open label, blinded endpoint (PROBE), non-inferiority study to be conducted in New Zealand and Australia.

**Study Subjects**

342 subjects presenting to the Emergency Department (ED) with a first primary spontaneous pneumothorax will be recruited, aiming for adequate follow-up of at least 274 participants.

**Inclusion criteria**

- Primary spontaneous pneumothorax that is 32% or larger by the method of Collins,\textsuperscript{31} that is a “sum of interpleural distances” (A + B + C) of 6 cm or greater (Figure 1).
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 (e.g. nocturnal symptoms) within the last two years.

- Coexistent haemothorax (i.e. spontaneous haemopneumothorax).

- Bilateral pneumothorax.

- Instability suggesting tension pneumothorax; systolic BP (SBP) <90 mmHg, mean arterial pressure (MAP)<65 mmHg or HR ≥ SBP (i.e. shock index HR/SBP ≥1).

- Age <14.

- Age >50 (due to a higher incidence of underlying lung disease, i.e. secondary pneumothorax).

- Pregnancy at time of enrolment (all women of reproductive age should 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 interventional or conservative management. To maintain allocation concealment subjects will be randomised in real time, stratified by study site, using an adaptive biased coin (Urn) technique to maintain balance allocation at each site. The University of Western Australia will host a web-based randomisation system (Filemaker Server Advanced, Filemaker Inc., Santa Clara, California).

Study Procedures

General management (all patients)

1. Oxygen as required (if SpO2 <92% on room air)

2. Initial analgesia (commenced prior to CXR if possible) if required:
   - Mild-moderate pain; paracetamol 1g orally PLUS a non-steroidal anti-inflammatory drug (NSAID), e.g. ibuprofen 400-800 mg orally, if there are no exclusions to NSAID.
Severe pain; paracetamol and a NSAID as for mild-moderate pain PLUS intravenous morphine with an initial bolus of 0.1 mg/kg (5-10 mg) with further 2.5 mg doses titrated to effect, followed by one dose of oral narcotic (e.g. oxycodone 5mg orally).

Conservative Treatment Protocol (Figure 2)

1. Observe for 4-hours then repeat CXR prior to discharge from the ED.
2. Prior to discharge, walk the patient around the ED to ensure that they are capable of undertaking routine activities of daily living.
3. Switch to the interventional protocol if either:
   a) Significant symptoms persist despite adequate analgesia:
      i) Chest pain and/or dyspnoea that is likely to prevent routine activities of daily living (bathing, going to toilet, etc.) or such that the patient is unwilling to continue conservative treatment.
      ii) Systolic BP <90 mmHg, HR ≥ SBP, respiratory rate >30/min, SpO₂ <90% on room air.
   b) The repeat CXR shows the pneumothorax is increasing in size AND there has been a trend in observations to suggest the development of tension. Note that an apparent increase in pneumothorax size on CXR does not necessarily require intervention if the patient’s clinical condition has improved or has remained stable.
4. Prescribe discharge analgesia according to patient requirements while in ED: Paracetamol 1g qid, +/- NSAID (e.g. ibuprofen 400mg tds) +/- a short supply of oral narcotic (e.g. oxycodone 5mg qid pm).
5. Provide written discharge instructions; these include procedures to follow in the event of deterioration and advice not to scuba dive or fly.
6. If at any stage during follow-up the patient has significant symptoms (as defined above) the investigator may elect to switch to the interventional protocol.

**Figure 2. Flow diagram: Conservative treatment**
Interventional Treatment Protocol (Figure 3)

1. Attempt aspiration using a small bore (≤12F) Seldinger-style chest drainage device* as follows:
   a) Insert in either the 2nd intercostal space mid-clavicular line anteriorly, or the safety triangle 
      laterally.
   b) Attach to an underwater sealed drain. Do not apply suction.

2. Repeat CXR 1 hour after insertion: If drainage is successful, (residual pneumothorax now small 
   with sum of interpleural distances <6 cm and reduction of symptoms if present initially and 
   underwater drain no longer bubbling) close the drainage device (using three-way tap) and 
   observe for 4 hours.

3. Repeat CXR 4 hours after closing the three-way tap. If the pneumothorax size is stable and the 
   patient remains clinically stable:
   a) Remove the small bore drainage device
   b) Prescribe simple analgesia (ibuprofen/paracetamol) for residual symptoms
   c) Provide written discharge instructions; these include procedures to follow in the event of 
      deterioration and advice not to scuba dive or fly

4. If aspiration is not successful or the pneumothorax recurs under observation:
   a) Open three-way tap and recommence underwater seal drainage
   b) Admit under Respiratory Medicine or an appropriate inpatient team (General Medicine or 
      Cardiothoracic). Subsequent interventions will be at the discretion of the treating physician. 
      Prior to discharge a CXR is to be performed after removal of all chest drains/catheters.

5. Clinician decision regarding use of timing of drain clamping or removal to be accommodated 
   within this protocol. Variations in local practice to be noted.

---

A randomised controlled trial of conservative versus interventional treatment of primary spontaneous pneumothorax
Version 5, 6.05.2014
Page 5 of 15
Follow up (all subjects)

a) 24 - 72 hours Follow-up
   • For discharged patients there will be a safety review at 24-72 hours (usually this will be an ED role).
   • For admitted patients a visit or telephone call to the ward will be made to carry out the follow-up assessments.
   • Or when these 2 options are not available; the completion of the follow-up questionnaires will be carried out over the telephone by the study state coordinator.

b) 2 – 8 Week Follow-up
   • Repeat CXR at two weeks, four weeks and eight weeks until pneumothorax resolution.
   • Where attendance at follow up appointments is not possible, completion of the follow up questionnaires will be carried out over the telephone by the study state co-ordinator.
   • Spirometry (FEV1, FVC, height and weight) after pneumothorax resolution.

c) 6 – 12 Month Follow-up
   Phone calls at 6 and 12 months with completion of the follow-up questionnaires with search of Clinical Information Systems and review of admission/ED attendance records and notes, if available.

d) 1 – 5 Years Follow-up
   Annual phone calls for up to 5 years with completion of the follow-up questionnaires and search of Clinical Information Systems and review of admission/ED attendance records and notes, if available.

Study measurements (all subjects)

• Age, sex, ethnicity, occupation and smoking history, convalescent FEV1 and FVC
• Date/time of onset, presentation, randomisation and discharge
• Calculation of pneumothorax size using the method described by Collins et al\cite{19} each time a CXR is performed. A single reporting radiologist will perform a blinded interpretation centrally, on large batches of de-identified CXRs presented in random sequence without date/time stamps to minimise any association between intervention and final outcome.
• Chest pain (verbal analogue) and dyspnoea (Borg scale) at each study contact; times of last chest pain and dyspnoea and last analgesia
• All procedures including date/time of each procedure and date/time of cessation/removal where relevant.
• Predefined complications /Adverse Events (AE):
  1. Tension pneumothorax
  2. Haemothorax
  3. Trauma to heart, liver, spleen or gut
  4. Foreign body in chest wall
  5. Foreign body in chest cavity
  6. Infection- skin and subcutaneous tissues treated with antibiotics
  7. Infection- empyema treated with antibiotics
8. Infection - pneumonia treated with antibiotics
9. Sepsis (likely infection and ≥2 of; temp >38 or <36, HR>90, RR>20, WCC>12 or <4)

- Other complications / Adverse Events (AE)
- Numbers of CXRs and chest CTs performed
- Details of unplanned attendances relating to pneumothorax until 8 weeks after enrolment. Patient satisfaction at 8 weeks
- Proportion of usual days of work or study lost at 8 weeks
- Pneumothorax recurrence

**Note:** For the purpose of defining pneumothorax recurrence, the time of resolution of the initial pneumothorax will be the time of the first CXR showing complete resolution at least 24 hours after the removal of all catheters/drains (generally no earlier than the 2-week review). Any re-accumulation prior to this will be attributed to the initial pneumothorax (i.e. ongoing leak) rather than a recurrence.

**Adverse Event Reporting**

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition. It does not necessarily have to have a causal relationship with treatment.

All AEs occurring during the course of our treatment and initial follow-up (i.e., until resolution or 8 weeks, whichever is longest) will be reported with the following exceptions that are considered to be ‘Anticipated Events’. These normally occur during treatment for primary spontaneous pneumothorax and are already being systematically assessed by the study as pre-defined outcomes:

- Chest pain
- Shortness of breath
- Prolonged drainage or VATS pleurodesis (unless complications of these procedures occur)
- Recurrence of pneumothorax
- Switching from conservative to interventional management
- Decision to abort intervention prior to pneumothorax resolution

However, should the severity of one of these events be such that it meets the criteria for a SERIOUS adverse event (for example necessitates a hospital admission) then this event should be reported as a Serious Adverse Event (SAE) and the expedited reporting timeframes apply.

A Serious Adverse Event (SAE) is defined as,

- Any AE which results in death
- Immediately life threatening, results in persistent or significant disability / incapacity, requires or prolongs patient hospitalisation
- A congenital anomaly / birth defect
- 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 SAE definitions.

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 on the ‘Adverse Event’ CRF.
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 study procedure and the AE.
- No: There is no reasonable causal relationship between the study procedure and the AE.

SAEs are to be reported to both the local ethics committee AND the study coordination centre 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.

Patients who are eligible but do not consent to study participation
Patients who are eligible but decline participation in the trial will be asked to allow us to monitor the outcomes of their chosen treatment, using the same follow up protocol as we will use in the trial. A specific consent form, allowing access to relevant medical records, will be provided for this purpose. Data from these patients will be used to identify any potential impact of patient preference on the study outcomes, as well as providing a larger number of cases to analyse the safety of each approach.

Genetics of Spontaneous Pneumothorax sub-component (APPENDIX 1)
This sub-component is optional for sites willing to be involved in collection of a DNA blood sample that is to be collected at any point throughout participant involvement in the study. Refer to appendix A for full protocol of this sub component.

Statistical Analysis

Primary outcome
- Proportion of subjects with complete lung re-expansion by 8 weeks.

Secondary outcomes
- Persistent air leak, defined by the presence of a chest drain/catheter in situ for 3 days or longer.
- Pneumothorax recurrence.
- Time to symptomatic recovery, defined as: discharge from hospital AND resolution of symptoms AND cessation of analgesic medication.
- Complication of therapy, defined by any predefined complication listed above.
A non-inferiority approach to analysis of the primary outcome (i.e. one-tailed alpha=0.05) will be used. 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). Per-protocol analyses will also be performed.

It will not be possible to blind local researchers to treatment allocation during the study, however the primary outcome (resolution on CXR) will be highly objective.

**Power calculation**

A sample size of 274 has been chosen 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. 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 is highly desirable to patients. High study power is recommended for non-inferiority studies such as this. Allowing for a dropout rate of 20% gives our recruitment target of 342 participants.

An important secondary outcome variable is the rate of recurrence by twelve months. A sample size of 274 has greater than 90% power, two-sided alpha of 5%, to detect an absolute difference of 20%, which represents a 5% recurrence rate in the conservative treatment group compared to 25% for invasive treatment.

**Source documents and data audit**

Original datasheets will be kept at each site in a secure location by the site investigator. At the completion of each section (patient review) these will be faxed to a coordinating centre (Medical Research Institute of New Zealand or Royal Perth Hospital) for data entry. A member of the Steering Committee or nominee (Research Nurse) will audit the first 3 cases at each site and 10% of subsequent cases with reference to the original medical record. The study will be conducted according to the standards of Good Clinical practice (GCP).

**Steering Committee**

An international Steering Committee is responsible for study design and management, analysis and write-up. It comprises three Emergency Physicians, five Respiratory Physicians, a Biostatistician and a Radiologist.

**Data Monitoring and Safety Committee (DMSC)**

An international Data Monitoring and Safety Committee (DMSC) will be formed. This will consist of at least two Emergency Physicians and two Respiratory Physicians and a Statistician who are not members of the study Steering Committee. They will not be involved in the study in any way. It is imperative that the study confirms the safety of the treatment approaches being compared as well any differences in the primary outcome. For this reason the study will continue to completion unless significant safety concerns arise. The DMSC will halt the study and notify the lead ethics committee(s) if they identify protocol safety issues that require immediate attention prior to further enrolments.
The DMSC will review all serious adverse events (SAEs), as well as cases with any of the following:

- Unplanned representation(s) and prolonged admissions longer than 1 week
- Interventional procedures (if subject initially allocated to conservative management)
- Any reported complication(s)

**Trial registration**

The study is registered with the Australian New Zealand Clinical Trials Registry (ANZCTR), registration number ACTRN12611000184976.

**Timeline**

We will test study procedures by starting enrolments at pilot sites in Australia and New Zealand during 2011. The study will then run at all sites for 5 years starting in 2012. Recruitment of study participants will occur over 4 years with a subsequent five year follow up period.

**Outcomes and Significance**

PSP is one of the most common conditions of the pleura to affect young people and adolescents. In the majority of cases the current interventional approach is associated with invasive procedures including surgery (all with the risk of pain and complications) and hospital admission resulting in time away from work, study, or childcare duties. This study will significantly increase our understanding of PSP and its optimal management. If allowing the lung to remain collapsed initially results in improved healing of the pleural defect and lower recurrence rates then this study will contribute to improved outcomes and a reduction in the morbidity associated with current treatment.

This will be the largest randomised controlled trial investigating the initial management of PSP performed to date and will have a global impact whatever the findings, being the first high grade evidence for how to treat PSP. If conservative management is demonstrated to be safe and effective it will lead to a major change in current medical practice and international consensus guidelines.
REFERENCES

29 Maskell NA, Medford A, Gleeson FV. Seldinger chest drain insertion: simpler but not necessarily safer. Thorax 2010; 65:5-6
APPENDIX 1

THE GENETICS OF SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax is usually an isolated event, when it occurs in an individual without pre-existing lung disease. Familial spontaneous pneumothorax is much rarer and was first reported by Faber in 1921. Spontaneous pneumothoraces have also been described as the presenting feature of inherited disorders such as Marfan's syndrome[1], Ehlers–Danlos syndrome[2], alpha 1 antitrypsin deficiency[3], tuberous sclerosis and Birt–Hogg–Dube (BHD) syndrome[4]. Broadly speaking these syndromes are associated with lung cysts or emphysema and it is these structural abnormalities that predispose to pneumothorax. Recurrent pneumothorax is particularly common in BHD (50 times more common than general population) and its frequency appears to vary with the type of underlying mutation in the Folliculin gene (FCLN). Penetrance of this and other features of BHD varies[5], and the role of other genetic modifiers remains unknown. Genetic modifiers of the pneumothorax phenotype have been reported in lymphangioleiomyomatosis (LAM)[6] – another cystic lung disease. Furthermore the incidence of FLCN or other relevant mutations in spontaneous pneumothorax remains unknown.

Preliminary data from the lung of patients with pneumothoraces and controls suggests that expression of various matrix metalloproteases (MMPs; Figure 1) differs, implying a role for MMPs in pathogenesis. MMP1, 3[7], 9 and 12[8] have both been associated with emphysema, MMP1 and 9 being specific to upper zone disease[9-10].

Understanding the risks that underlie spontaneous pneumothorax may have implications for patients’ subsequent investigation and management; for instance BHD patients have an increased risk of renal cancer[11], and steps to screen for this might be appropriate. Counselling on the risk of recurrence could also be undertaken, based on genetic profile. Finally, targeted treatment might be possible for some individuals.

Figure 1: MMP9 staining in lung tissue

A control subject is shown on the left and a patient on the right; MMP9 is more highly expressed in the pneumothorax patient.

This has obvious parallels to the upper zone blebs seen in some spontaneous pneumothorax patients, adjacent to which MMP1 positive macrophages can be seen (Figure 2).
Figure 2: MMP staining co-localises to blebs in pneumothorax
MMP1 positive macrophages appear close to a bleb structure in the slide shown on the left. On the right the picture shows the appearance of such a bleb during VATS thoracoscopy.

Aims
1) Assess the frequency of mutations in FCLN in spontaneous pneumothorax
2) Investigate the FCLN pathway and other selected candidate genes for association with pneumothorax
3) Explore the concept of genetic modifiers of respiratory phenotype in BHD

Methods
All patients enrolled to the trial will be approached for DNA collection; if consent is granted a single EDTA tube of blood will be taken and stored at -80°C, with a view to batch transfer of samples to the UK centre (Queen Elizabeth Hospital, Birmingham) in due course. We will undertake a case-control candidate gene study comparing patients enrolled to the trial, plus patients with pneumothoraces admitted to our UK collaborator’s hospital, or collected in existing work (UK total =200) matched to healthy controls from the 1958 birth cohort[12]. DNA will be extracted by a modified Nucleon Bacc II method, quantified using Picogreen, genotyped using TaqMan, and results assessed using logistic regression, accounting for age and smoking status, as described in our previous published work[13]. Replication will be carried out in a large familial BHD dataset, seeking genetic modifiers of the pneumothorax phenotype in this group. All DNA work will be undertaken in the UK. Subsequent studies there will assess the underlying mechanisms of disease using in vitro models.

Candidate genes predefined for study are: FLCN, SERPINA1, MMP1, MMP3, MMP12, MMP9, MMP2, MMP8, FBN1, COL3A1, COL1A1 and COL1A2. These have been chosen as they either cause a syndrome associated with pneumothorax, or have been implicated in our prior mechanistic work. All genes will be tagged using data from HapMap (minor allele frequency (MAF) >0.1, r2>0.8), in order to pick up all common variation in the gene, as well as typing known disease causing mutations in FCLN. Assuming α=0.05, MAF equivalent to the mean of the selected tag SNPs (0.25), 500 cases and 500 controls we will have 80% power to detect a variant conferring an odds ratio of 1.33 of primary spontaneous pneumothorax. We will also explore the possibility of sequencing FCLN (funding dependent) in the spontaneous pneumothorax patients. Genome-wide association study would not be appropriate as it would be underpowered.
REFERENCES


