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The Pneumothorax And Symptom Evaluation (PASE) Study:

Bendopnoea in patients with pneumothorax

1 Trial Details	
Protocol/Clinical Trial Title:	**The Pneumothorax And Symptom Evaluation (PASE) Study: *Bendopnoea in patients with pneumothorax***
Protocol Number (Version and Date):	Version: 1/ Date: 06 September 2023
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1.1 Lay Summary

Pneumothorax (a collapsed lung) occurs when air leaks from the lung and accumulates between the chest wall and the lung, resulting in partial lung collapse. The build-up of air may impair diaphragm function (the muscle that helps us breathe). The mechanism of breathlessness in pneumothorax is unclear, and symptoms can vary between patients. Some patients present with minimal or absent symptoms, whilst others experience distressing breathlessness and pain. Sometimes tubes may need to be inserted between the ribs to drain the collected air and help the lung reinflate, and occasionally surgery is required to stop the leak.

Currently, the effect of the accumulated air in the pleural space and its association with diaphragmatic function and symptoms of breathlessness is not well understood. Bendopnoea (breathlessness when bending forward) is an evolving clinical symptom that has been demonstrated as clinically useful in some heart and lung conditions. Whether bendopnoea is present in patients with pneumothorax, and its potential clinical usefulness has not yet been investigated.

The PASE study is a pilot study to explore the incidence and clinical relevance of bendopnoea in patients with pneumothorax and may provide better understanding of breathlessness in pneumothorax.

2 Rationale / Background

Pneumothorax is a condition characterised by the presence of air in the pleural space between the lung and chest wall (1). This abnormal accumulation of air can cause partial or complete collapse of the lung, and the patient can experience breathlessness and chest pain (2, 3).

Pneumothorax can be classified as spontaneous or traumatic (including from medical procedures). Bendopnoea is a simple and safe bedside test that requires patients to bend forward and report symptoms of breathlessness. It does not require the use of any equipment or specific resources and can be completed within 60 seconds, therefore the test can be easily replicated during routine assessments in all settings.

In patients with pneumothoraxes, the level of breathlessness varies amongst patients and the precise mechanism of breathlessness in pneumothorax remains unknown. In contrast, breathlessness in patients with pleural effusion is now linked with diaphragmatic dysfunction due to presence of pleural fluid. Whether that holds true for pleural air in pneumothorax is also unknown. Bendopnoea is emerging as a clinically useful symptom related to patient outcomes in many cardiorespiratory diseases, however, it has not yet been explored in pleural disorders. Our literature review found bendopnoea is a clinical biomarker in patients with advanced heart failure (HF) (7, 8) and with pulmonary arterial hypertension (PAH) (9) that is prognosis (7, 8), worse functional capacity (9), haemodynamic characteristics (9) and right ventricular function (9).

The incidence of bendopnoea has not yet been reported in patients with pneumothorax (Aim 1), including the correlation of bendopnoea with pain, breathlessness, size of pneumothorax and respiratory physiological parameters (Aim 2). In the context of pneumothorax, the clinical usefulness of bendopnoea as a predictor of outcome is yet to be explored (Aim 3).

3 Trial Aims / Objectives / Hypotheses

The PASE study will explore the incidence of breathlessness on bending forward (bendopnoea) in patients with pneumothorax and whether this is associated with symptoms, size of pneumothorax, physiological parameters and the clinical outcome.

We hypothesize that bendopnoea:

1. Is prevalent in individuals with pneumothorax
   a) Associated with higher levels of breathlessness,
   b) Reflect size and types of pneumothoraxes, and
   c) Correlated with clinical outcome (i.e., response to drainage/lung reinflation).

Study Aims and Outcomes:

In a prospectively recruited unbiased/unselected cross-sectional cohort of patients with pneumothorax, this study will explore the:

1. *Incidence of bendopnoea in this population,*
   a. Correlation of the associated symptoms (pain and breathlessness) to the severity of bendopnoea and the size of pneumothorax; and
   b. Correlation with clinical outcome (i.e., response to drainage/lung reinflation).

2. *Pathophysiological basis of bendopnoea* by*:*
   a. Determining the relationship of bendopnoea with breathlessness scores, pain scores and physiological parameters (e.g. oxygen saturations).

The above will be performed in all patients at baseline and for patients where air drainage is indicated as per standard care, once the drain is removed.

4 Trial Design

4.1 Study Endpoints

Overall:

1. To determine whether bendopnoea is present in patients with pneumothorax,
2. To determine whether bendopnoea is associated with clinical symptoms (pain and breathlessness), the size of pneumothorax and respiratory physiological parameters; and
3. To determine whether bendopnoea is correlated with clinical outcome (i.e., response to drainage/lung reinflation).

4.2 Type of design

PASE is a multi-centre prospective study.

4.3 Study Duration

The study will enrol participants for a period of 24 months. This is based on the number of potentially suitable participants seen in the recruiting centres (~2/month).

4.4 Trial Termination

Early trial termination may occur for the following reasons,

a. The Data Safety and Monitoring Committee has significant concerns and advise 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.

4.5 Data identification

Each study patient will have a unique study identification code created following informed consent which will comprise their first name and last name initials and a consecutive number generated at the time of randomisation. Study participants will have individual trial notes created separate to the participant's medical records. These will be kept in a secure (locked) filing cabinet in a locked office in the SCGH Respiratory Department.

5 Source and Selection of Participants

5.1 Source of Participants

This study will enrol 50 consecutive eligible patients with pneumothorax from the pleural service of Australian centres. A screening log will be maintained. Patients who require drainage/lung reinflation as part of their clinical care will be assessed before and after reinflation. All participants will receive standard care for their conditions as per their treating clinicians. From the time of signing consent, participants will remain in the study for 3 months.

5.2 Participant inclusion criteria

- In- and out-patients referred for assessment of a unilateral spontaneous (primary or secondary) pneumothorax or iatrogenic pneumothorax.

5.3 Participant exclusion criteria

- Pneumothorax with a concurrent pleural effusion > 1cm in size
- Hemodynamically unstable (systolic blood pressure of <90 mmHg, heart rate in beats per minute greater than or equal to systolic blood pressure in mmHg, respiratory rate of >30 breaths per minute, and Spo2 of <90% on room air)
- Age <18 years
- Mechanical limitations in bending forward (*e.g.,* spinal conditions or large abdominal mass)
- Pregnancy/lactation
- Inability to consent and/or comply with protocol

5.4 Participant withdrawal criteria

Participants can withdraw at any time from the study and do not need to provide a reason. 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 attending study visits 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. Withdrawn participants will not be replaced. If considered clinically necessary, withdrawn participants will be asked to return to clinic for safety follow-up appointment(s).

6 Treatment of Participants

6.1 Intervention

The following parameters will be assessed using a range of validated tools for all patients

1. At baseline (pre drainage/lung reinflation) and,
2. For those proceeding to drainage, once the drain is removed.

Bendopnoea is assessed:

1. In a qualitative manner (as modified from Baeza-Trinidad et al (11)) with the following question:
    a. *"Since the onset of your symptoms, how has shortness of breath when bending forward impacted your day-to-day activities?"*
        i. **No limitation:** I was not troubled by breathlessness when bending forward
        ii. **Mild:** I felt breathless when bending forward and performing an activity (e.g., tying shoelaces) but can still perform activities without limitation or rest.
        iii. **Moderate:** I had to stop and take breaks from bending forward to complete what I wished to do (e.g. I have to bend down several times to complete tying the laces of both shoes).
        iv. **Severe:** I was too breathless to bend forward
    b. After the air drainage procedure, the question will be phrased: *"since the procedure, how does shortness of breath when bending forward impact your day-to-day activities?"*

2. With objective testing, as per published studies (9, 11, 12):
    a. Patient sitting in a chair is instructed to bend forward at the waist and aim to touch his/her ankles and maintain this position for up to 60 seconds. Patient will inform the investigator as soon as breathlessness occurs, and the time of onset of bendopnoea recorded.
    b. Bendopnoea is recorded as:
        i. Time to breathlessness, and
        ii. Present or absent during the test.

Degree of breathlessness and impairment on functional activities:

Breathlessness will be measured using a 100mm visual analogue scale (VAS) anchored by "no shortness of breath at all" and "maximum shortness of breath" (13). VAS scores have been used previously to measure breathlessness in this population (14). The mean of the VAS scores measured by two independent researchers will be documented.

Degree of pain and impairment on functional activities:

Pain will be measured using a 100mm visual analogue scale (VAS) anchored by "no pain" and "worst pain" (15). The mean of the VAS scores measured by two independent researchers will be documented.

Patient characteristics Breathlessness can be a result of concurrent illnesses (e.g., heart failure, COPD etc) and intrathoracic (e.g., pulmonary emboli) or extrathoracic factors (e.g., muscle wasting) which will be captured from case notes. Height, weight and body mass index will be recorded. Cardio-pulmonary status (respiratory and heart rates, blood pressure and oxygen saturation) and the aetiology of the pneumothorax will be recorded.

Pneumothorax Characteristics The size of the pneumothorax will be measured on standard erect PA inspiration chest radiographs (CXR) with the Light Index (1) and Collins Method (16). The Light Index measures the average diameter of the lung and the hemithorax, cubing these diameters, and finding the rations (1) whereas the Collins Method calculates the 'sum of interpleural distances' which estimates the pneumothorax size (16).

7 Assessment of Safety

7.1 Risks and benefits

Summary of known and potential risks and benefits, if any, to research participants.

7.2 Safety

Pleural interventional procedures will be performed as necessary as part of standard of care. Standard medical care and any drainage procedures (including needle aspiration, chest tube insertion or surgery) remains the responsibility of the treating physician of the patient. The patient will only be enrolled if a consultant physician feels it is safe to proceed.

7.3 Data and Safety Monitoring Board

The Data Safety Monitoring Board is set up 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 DSMB. 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 DSMB 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 DSMB provides recommendations to the lead investigators, who oversees the study and determines whether the study should continue or be suspended or terminated.

7.4 Adverse Event (AE) Reporting

All AEs relating to the trial investigations, serious and non-serious, will be fully documented on the appropriate CRFs. For each AE, the investigator will provide the onset, end, intensity, treatment required, outcome, seriousness and action taken. The investigator will determine the relationship of the investigative 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.

An 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 AE's relating to the investigations occurring during the course of the clinical trial (ie; from signing the informed consent until death or the end of the study follow up period, whichever

comes first) will be collected and documented by the investigator according to the specific definitions and instructions detailed in the 'Adverse Event Reporting' section of the Trial Master File. Cases will also be reported if a causal link between the AE and the trial investigations is suspected but not confirmed. Any event that meets the criteria for a Serious Adverse Event (SAE), as defined below, reported as an SAE.

A **Serious Adverse Event (SAE)** is defined as any AE that,

- results in death
- is life-threatening
- results in persistent or significant disability / incapacity
- prolongs hospitalisation by ≥24 hours (i.e. unexpected overnight admission)
- is deemed serious for any other reason such that it is thought to jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above SAE definitions.

SAEs are to be reported immediately to the local ethics committee using the Serious Adverse Event Report Form including a documented causal relationship assessment and providing as much detail regarding the SAE as possible.

8 Data Management, Statistical Analysis and Record Keeping

8.1 Sample Size

This study will aim to recruit 50 participants with spontaneous (primary and secondary) pneumothorax and iatrogenic pneumothorax over 24-months. This number is achievable in the proposed timeframe and accounts for those who decline to take part in the study. The study may expand if major numbers are observed.

8.2 Statistical Plan

This is a pilot study to determine whether bendopnoea is present in patients with pneumothorax, and whether it correlates with clinical symptoms (pain and breathlessness), the size of the pneumothorax and respiratory physiological parameters. It also aims to determine whether bendopnoea is correlated with clinical outcome (i.e., response to drainage/lung reinflation).

Descriptive statistics of baseline characteristics of patients and measured bendopnoea, pain and breathlessness responses will be provided. The magnitude and direction of the change between the baseline and post-intervention measurements (e.g., responses in bendopnoea, pain and breathlessness) will be estimated. Statistical modelling will be applied to determine the correlation of bendopnoea to symptoms, the size of the pneumothorax, physiological parameters and clinical outcomes.

8.2 Statistical Plan Deviations

Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate). For further information refer to NHMRC "Reporting of Serious Breaches of Good Clinical Practice (GCP) or the Protocol for Trials Involving Therapeutic Goods" 2018.

8.3 Selection of participants for analyses

All patients who fulfil the criteria and consent for the study will be included in the analyses, to minimise/exclude selection bias. Our team includes experienced biostatistician Professor Kevin Murray (University of Western Australia) for study planning and data analyses.

8.4 Data Management

8.4.1 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site. Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained (Source Document Verification). The investigator may need to also investigate any inconsistencies using medical records. These medical records will be available to the investigator as one of the patient's treating physicians.

8.4.2 Trial Master File (TMF)

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

8.4.3 Data Sharing

De-identified data from paper case report forms is being transposed into the study REDCap database. The dataset will be exported for analysis at the end of the study from REDCap to an Excel spreadsheet for the designated study statistician. Consent to this study is extended so data collected from this study will be used in future related studies such as meta-analysis study involving other studies of the PLEASE series. Those wanting access will need to contact the study CPI and provide an outline of the reason that data access is required. If this is deemed legitimate an amendment will need to be made to state that the data are to be made available to the individual and include the institution where the data will be held and archived. Where possible a virtual transfer of data will be made so that the primary dataset remains at the original institution and is managed according to local guidelines.

8.4.4 Data Archival

Data anonymisation is carried out at source. Data cleaning is carried out following data lock at the end of the study and following completion and resolution of all data queries. The cleaning is essentially carried out by the nominated statistician.

The long-term storage is onsite. If these buildings are to be used for other reasons or the building are to be pulled down, then the backup position would be archive with Iron Mountain

and set up a contract accordingly. Standard operating procedures (SOPs) for archiving paper records/ and TMF will be followed. An electronic archive of the study will also be created and retained in a named access only section of the SCGH W drive. The study data will be retained for 15 years.

9 Monitoring / Audit

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.

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.

10 Quality Control and Quality Assurance

10.1 Data Quality Control and Reporting

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

10.2 Data Quality Assurance

The study will be conducted according to the principles of ICH GCP, National Statement and local SOPs The accuracy of the data will be verified by comparing study data to source documents. Medical records and progress notes will be kept accurate and up to date and available at all times for inspection in the event of an audit.

11 Ethics

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

12 Budget, Financing, Indemnity and Insurance

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. Any shortfalls in funding will be covered by CPI-Lee's research funds at the Institute for Respiratory Health.

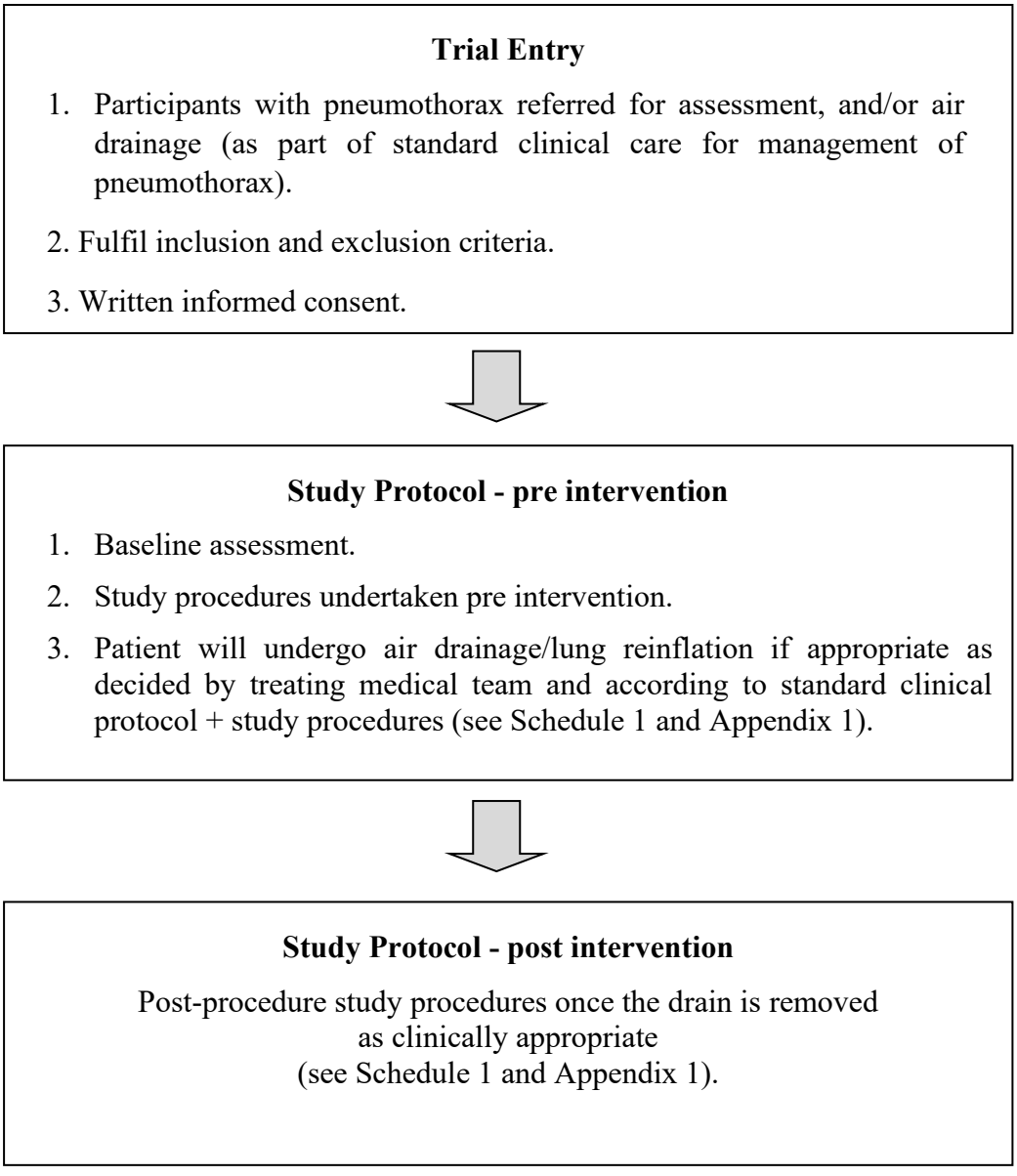
13 Publication

No study results will be formally published prior to completion of the final HREC study report.

14 Appendices

Study Flowchart

Trial entry, trial treatment and post procedure care.



Schedule 1

Procedure	**Duration (mins)**	**Visit 1 (Day 0)**	**Visit 2 (Once drain is removed)**
Informed consent	10	x	
Baseline observations	5	x	
VAS score breathlessness	1	x	x
VAS score pain	1	x	x
Bendopnoea test i) semi-quantitative question ii) objective test in chair	5	x	x

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