Received: 2 May 2024 | Accepted: 29 May 2024

DOI: 10.1002/rcr2.1410

CLINICAL TRIAL PROTOCOL

Respirology Case Reports | WILEY

The third PLeural Effusion And Symptom Evaluation (PLEASE-3) study: Bendopnoea in patients with pleural effusion

Bapti Roy[1,2,3] | **Bianca M. Iacopetta**[1,2] | **Carolyn J. Peddle-McInytre**[1,2] | **Michaela Donaghy**[4] | **Matthew Ing**[1,5] | **Ai Ling Tan**[1] | **Y. C. Gary Lee**[1,4,5]

[1]Pleural Medicine Unit, Institute for Respiratory Health, Perth, Western Australia, Australia

[2]Exercise Medicine Research Institute, School of Medical and Health Sciences, Edith Cowan University, Perth, Western Australia, Australia

[3]Department of Respiratory and Sleep Medicine, Westmead Hospital, Sydney, New South Wales, Australia

[4]Department of Respiratory Medicine, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia

[5]School of Medicine, University of Western Australia, Perth, Western Australia, Australia

Correspondence
Y. C. Gary Lee, Pleural Medicine Unit, Institute for Respiratory Health, 533 Perkins Building, QE II Med Ctr, Perth, WA 6009, Australia.
Email: gary.lee@uwa.edu.au

Funding information
Sir Charles Gairdner Research Advisory Council, Grant/Award Number: MRGP21-22_20_Pfr Y C Gary Lee; Sir Charles Gairdner Research Advisory Council research

Associate Editor: Claude Farah

Abstract

Background: Pleural effusions often cause disabling breathlessness, however the mechanism is unknown. Patients with pleural effusions are subjected to pleural fluid drainage on a 'trial and error' basis, as symptom relief varies. This population commonly complain of bendopnoea (breathlessness on bending forward) which has not been investigated. Our pilot data found bendopnoea was significantly associated with presence of pleural effusion. The PLEASE-3 study will evaluate bendopnoea as a screening test for effusion-related breathlessness, its predictive value of symptomatic benefits from fluid drainage and explore its underlying physiological mechanism.

Methods: PLEASE-3 is a multi-centre prospective study. Eligible patients are assessed at baseline (pre-drainage) and for patients undergoing drainage, up to 72 h post-procedure. Outcome measures include the prevalence of bendopnoea, its correlation with size of effusion and its predictive value of breathlessness relief after drainage. The relationship of bendopnoea with breathlessness, physiological parameters, functional capacity and diaphragmatic characteristics will be assessed. The study will recruit 200 participants.

Discussion: This is the first study to investigate bendopnoea in patients with pleural effusion. It has minimal exclusion criteria to ensure that the results are generalisable. The presence and clinical significance of bendopnoea in the context of pleural effusion requires thorough investigation. The post assessment of patients undergoing pleural fluid drainage will provide insight into whether the presence of bendopnoea is able to predict clinical outcomes.

Trial Registration

***Name of the registry*:** Australia New Zealand Clinical Trial Registry
***Trial registration number*:** ACTRN12622000465752.
***URL of the trial registry record for this trial*:** https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383639&isReview=true
***Date of registration*:** Registered on 24 March 2022.
***Funding of the trial*:** This study has received funding from the Sir Charles Gairdner Research Advisory Council research project grant. The study is sponsored by the Institute for Respiratory Health, a not-for-profit organisation.
***Name and contact information for the trial sponsor*:** Mr Bi Lam; Finance manager. Level 2, 6 Verdun Street, Nedlands WA 6009. t‖ + 61 8 6151 0877 e‖ bi.lam@resphealth.uwa.edu.au
***Role of sponsor*:** The funder is not involved in the planning of the study, gathering, analysing, and interpreting the data, or in preparing the manuscript.

KEYWORDS
bendopnoea, diaphragm dynamics, dyspnoea, pleural effusion

INTRODUCTION

Pleural effusions affect 60,000 Australians every year and can arise from a wide range of causes including cancer, heart and liver failure. Pleural effusions often cause disabling breathlessness. Drainage of the fluid can relieve symptoms, but the benefits vary among patients. The mechanism by which pleural effusion causes breathlessness remains unclear. A reliable method of identifying the patients likely to respond to drainage may help reduce unnecessary, painful procedures and their associated complications and healthcare costs.

The PLeural Effusion And Symptom Evaluation project aims address this knowledge gap. The recently published PLEASE-1 study,[1] was the largest study assessing factors that predict improvements in breathlessness. One-in-four of the 150 patients in the study did not improve post-drainage and the study showed strong evidence that pleural effusions cause breathlessness by impairing the functioning of the hemidiaphragm (main muscle of breathing) on the same side of the effusion by altering its shape and movement. Patients with abnormal hemidiaphragm movement pre-drainage were four times more likely to have improvement in breathlessness upon fluid drainage.

Bendopnoea (breathlessness on bending forward) is a common clinical complaint in patients with pleural effusion but has not been previously studied. Our pilot data found that bendopnoea was significantly associated with the presence of pleural effusion.

The PLEASE-3 study will aim to:

i. confirm that bendopnoea is significantly common in patients with pleural effusion, and can predict improvement in breathlessness after fluid drainage; and
ii. describe associations in respiratory physiological tests and ultrasonographic changes of the diaphragm associated with bendopnoea before and after pleural fluid drainage.

This study will evaluate the value of bendopnoea as a screening test for effusion-related breathlessness, its predictive value of symptomatic benefits from fluid drainage and explore the physiological mechanisms underlying bendopnoea.

Background and rationale

Pleural effusion refers to the pathological accumulation of fluid between the chest wall and lungs.[2] It affects 60,000 Australians a year especially those with cancers and heart, liver or renal failure. Breathlessness, often incapacitating, is the most common symptom and can significantly impair quality-of-life (QoL).

Most patients with pleural effusions are subjected to pleural interventions (e.g., thoracentesis and chest tube placement) to remove fluid for symptom relief. Pleural drainage procedures are costly and all drainage procedures induce pain and can have serious risks for example, haemorrhage, infection, pneumothorax, puncture of underlying liver or lung and death.[3] Concerns of the frequencies of pleural procedural complications are well documented.[4]

How pleural effusion causes breathlessness is unknown. Our literature review found that many studies on mechanisms of effusion-related breathlessness involved fewer than 35 patients and the results are conflicting.[5] Few studies have investigated how effusions cause breathlessness and no accurate predictors exist that can determine which patient will benefit from pleural drainage. In everyday practice, all patients are put through interventions on a 'trial-and-error' basis.

To address these important knowledge gaps, we initiated the PLeural Effusion And Symptom Evaluation series. The PLEASE-1 study,[1] was the largest ($n = 150$) of its kind and found that as many as 1-in-4 patients have no significant relief of breathlessness after undergoing invasive drainage (median drainage 1.7 L).[1] We showed, for the first time, that abnormal shape/movement of the ipsilateral hemidiaphragm is common and predicts (albeit imperfectly) improvement in breathlessness post-drainage.[1]

No reliable predictors exist to guide patient selection for drainage; currently all patients are subjected to invasive drainage to determine if their breathlessness improves. A simple, clinically reliable marker that can help predict effusion-related breathlessness and provide likelihood of symptom response after drainage will be a welcomed tool in day-to-day clinical practice (Aim 1).

We observed that patients with a pleural effusion commonly complain of breathlessness on bending forward (bendopnoea) which has never been reported as a symptom of pleural effusion in published literature. Prior investigations on bendopnoea relate to its biomarker role in cardiac failure, showing it occurs in severe (NYHA class IV) cases and is associated with increased mortality but the underlying mechanism of bendopnoea has never been established.[6–9] Increase in left ventricular filling pressures as well as pulmonary arterial pressures when bending forward in cardiac failure (along with increased intrathoracic and/or intra-abdominal pressure etc.) have been postulated.[7,8,10] These hypotheses alone fail to explain why breathlessness on bending forward occurs in some and not all patients with cardio-respiratory comorbidities (<50% of decompensated cardiac failure). Confounding factors, such as obesity-related raised intra-abdominal pressure and reduction in end expiratory volume, are inconsistently associated with bendopnoea in other populations.[11,12] The presence of diaphragmatic dysfunction (presumably related to upward displacement of abdominal contents and reduced activity of accessory muscles) has been hypothesised but never explored in bendopnoea.

Our previous data strongly support further investigation of the role of hemidiaphragm effects in the presence of a pleural effusion (Aim 2).

Objective

The PLEASE-3 study will specifically examine our novel clinical observation that patients with a pleural effusion often

complain of breathlessness on bending forward (bendopnoea), and that this symptom predicts treatment response.
We hypothesize that bendopnoea:

1. Is a useful clinical marker:
   a. Prevalent in individuals with pleural effusion
   b. More severe in larger effusions, and
   c. Able to predict symptom improvement after pleural fluid drainage;
2. Is associated with physiological, functional and diaphragmatic changes which improve following pleural fluid removal.

We will assess the usefulness of bendopnoea as a screening test for pleural effusion and in identifying patients who are likely to have symptomatic benefits following pleural fluid drainage.

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

1. *Role of bendopnoea as a clinical marker* by determining the
   a. Prevalence of bendopnoea in this population.
   b. Correlation of the prevalence and severity of bendopnoea with the size of pleural effusions,
   c. Improvement of bendopnoea after pleural fluid drainage,
   d. Predictive value of bendopnoea in relief of breathlessness after pleural fluid drainage.
2. *Pathophysiological basis of bendopnoea* by:
   a. Determining the relationship of bendopnoea with breathlessness scores, physiological parameters (e.g., spirometry and oxygen saturations) and function capacity (6-minute walk test, 6MWT),
   b. Correlating bendopnoea with abnormalities in the shape and movement of the diaphragm.

The above will be performed in all patients at baseline and in those undergoing a pleural drainage, up to 72 h post thoracentesis or when maximal drainage is reached in patients with chest drain insertion.

Trial design

PLEASE-3 is a multi-centre prospective study to evaluate the presence and clinical significance of bendopnoea in patients with pleural effusion.

METHODS

Participant screening, selection, and recruitment

The site principal investigator will screen patients with pleural effusion appropriate to be included in the study. Potential participants will be approached about the study and provided with the participant information and consent form to read and given time to ask questions to the study team. They will also be given time to discuss the study with family and carers, if needed. Eligible participants will be offered entry and enrolled after providing informed consent. Those patients who require pleural fluid drainage as part of their clinical care will be assessed before and after drainage. The site principal investigator will be aware of their dual role as the patients' primary physician and as a clinical researcher and where this patient dependency can be a potential conflict. All participants will receive standard care for their conditions as per their treating clinicians. Enrolment and screening logs will be maintained.

Study setting

This study will enrol consecutive eligible patients with pleural effusion from the pleural service of Australian centres. This trial will include 200 patients with pleural effusion.

Eligibility criteria

Eligibility criteria includes in- and out-patients referred to the Sir Charles Gairdner Hospital Pleural Service and the Respiratory Department of Westmead Hospital for assessment of a pleural effusion and/or pleural fluid drainage.

Exclusion criteria

Exclusion criteria includes age < 18 years, mechanical limitations in bending forward (e.g., spinal conditions or large abdominal mass), pregnancy/lactation and inability to consent or comply with protocol.

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).

Outcomes

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

1. At baseline (pre-drainage) and,
2. For those proceeding to pleural fluid drainage, up to 72 hours post drainage. For patients with intercostal catheter (ICC) or indwelling pleural catheter (IPC), this will be after the pleural fluid is completely drained.

Bendopnoea is assessed:

1. In a qualitative manner (as modified from Baeza-Trinidad et al.[6]) with the following question:
   a. *'In the last 7 days, how does shortness of breath when bending forward impact your day-to-day activities?'*
      i. **No limitation:** I was not troubled breathlessness when bending forward
      ii. **Mild:** I felt breathless when bending forward and performing 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 wish 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 pleural procedure the question will be phrased: *'how does shortness of breath when bending forward impact your day-to-day activity now?'*
2. With objective testing, as per published studies[6–8]:
   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 60 seconds. Patient will inform the investigator as soon as breathlessness occurs, and the time of onset of bendopnoea recorded.
   b. Bendopnoea is assessed:
      i. As a continuous variable (time to breathlessness) and
      ii. As present or absent during the test.

Degree of breathlessness and impairment on functional activities:

Breathlessness will be measured using a validated 100 mm visual analog scale (VAS) anchored by 'no shortness of breath at all' and 'maximum shortness of breath'.[13] VAS, has been successfully used in several of our RCTs on malignant effusion management (e.g., TIME-2,[14] -3[15] and AMPLE-1[16]) with the lower end of the 95% CI (14 mm) used as the *minimal clinically important difference.*

The impact of breathlessness on function

This will be measured with a standard 6-minute walk test performed by trained operators as per guidelines.[17] This is a well validated and commonly used measure.[18–20]

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 (heart rate and oxygen saturation) and the aetiology of the effusion will be recorded. Spirometric volumes (FEV_1 and FVC) will be performed according to the American Thoracic Society criteria.[21] Echocardiogram will not be requested specifically for this study; however if the patient has echocardiogram studies performed for their clinical need, the data will be recorded.

Pleural effusion characteristics. The *size* of the effusion will be graded semi-quantitatively on chest radiographs (CXR) using the scores (0 to 5) as published by Light et al.,[22] and as our lead investigators have used in prior publications.[1,16] The *volume of fluid drained* and its *biochemistry* (protein, LDH, pH, etc) will be recorded.

Evaluation of diaphragmatic dysfunction. Pleural ultrasound (B-mode and M-mode) will be performed at the bedside to assess both hemi-diaphragms using a real-time scanner with 3.5 and 12-MHz sector transducer (as per published methods[23–25]) in the upright position: to assess diaphragm shape (normal domed, flattened or inverted) and movement (normal, reduced or paradoxical).

Participant timeline

Participation flow is demonstrated in Figure 1 and time burden to patients in shown in Table 1.

Sample size

This study will aim to recruit 200 participants. This will be sufficient to encompass common causes of pleural effusions (e.g., malignant effusions and others from cardiac failure). It is anticipated that 50% (i.e., $n = 100$) will require pleural fluid drainage and the rest not, based on our previous studies (PLEASE-1 and -2). This number of participants will ensure effusions with a range of sizes (e.g. small, medium and large effusions), chronicity (e.g., acute and chronic) and aetiology (e.g., malignant, heart failure, and hepatic hydrothorax) are captured.

Recruitment

The study will enrol participants for a period of 24 months. This is based on the number of potentially suitable participants seen in the two recruiting centres (~3–8/week).

Data collection, management, and analysis

Data collection methods

Data from paper case report forms is being transposed into the study REDCap database. This will be de-

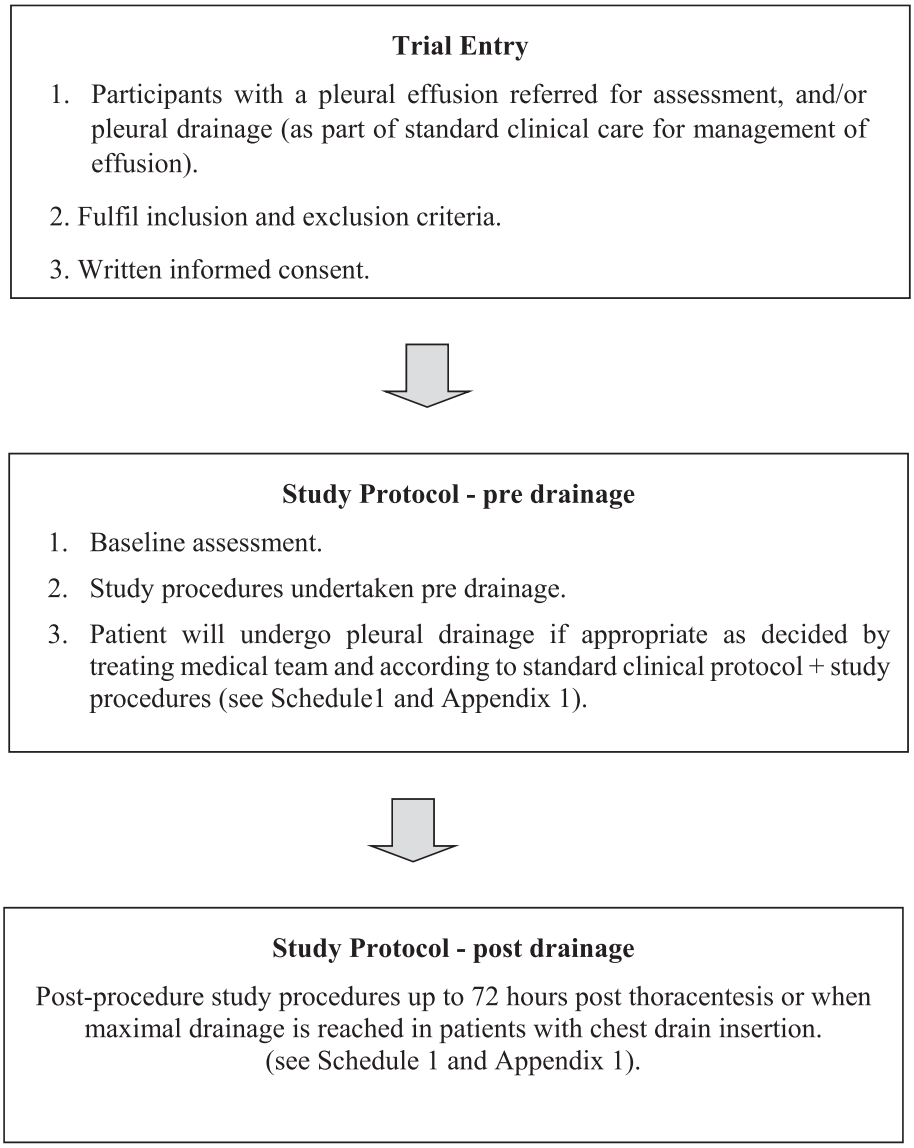

FIGURE 1 Study flowchart; trial entry, trial treatment and post procedure care.

TABLE 1 Patient time burden.

Procedure	Duration (mins)	Visit 1 (day 0)	Visit 2 (up to 72 h post thoracentesis/maximal drainage)
Informed consent	10	x	
Baseline observations	5	x	
VAS score	1	x	x
Bendopnoea test			
(i) semi-quantitative question	5	x	x
(ii) objective test in chair			
6-minute Walk Test (6MWT)	10	x	x
Spirometry	5	x	x
Pleural ultrasound[a]	5	x	x

[a]Only for patients where a pleural drainage is indicated as part of clinical care.

identified data. 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 comparing all studies in the PLEASE study 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 is 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.

Data management

All procedures for the handling and analysis of the data will be conducted according to the ICH GCP guidelines and the National Statement on Ethical Conduct in Human Research (2007)—*Updated 2018* and in accordance with local policies and procedures.

Data collected will be stored in line with the Australian Code for the Responsible Conduct of Research for clinical trials and local policy guidelines for research data archiving. Access to the final trial dataset will only be available to the research team at the lead site. Audits, if any, are usually carried out by an independent compliance monitoring officer.

Statistical methods

Descriptive statistics of baseline characteristics of patients and measured bendopnoea, breathlessness responses, functional capacity, pleural effusion characteristics and diaphragmatic dysfunction will be provided. The magnitude and direction of the change between the baseline and post-intervention measurements (e.g., responses in bendopnoea, breathlessness etc.) will be estimated. Statistical modelling will be applied to determine the correlation of bendopnoea to symptoms, functional capacity, diaphragmatic dysfunction, the size and characteristics of the pleural effusion and clinical outcomes.

Study power and significance

Pilot data

In a cross-sectional, prospective pilot study of in- and outpatients seen by the Pleural Services of SCGH, we found that 83% (19/23) of patients with pleural effusion reported the presence of bendopnoea compared with 12% (3/25) in randomly selected hospital staff with no known pleural diseases, $p < 0.00001$ (Fisher's exact test). In 8 patients with bendopnoea who underwent pleural drainages, all reported resolution or significant improvement of bendopnoea post-procedure. Therefore, the requested size of cohort of 200 will be more than sufficient in power – but is necessary to capture the range of clinically relevant subtypes of pleural effusions.

Monitoring

Data monitoring

This study will have site monitoring carried out by the lead site. Source data will be scrutinized 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.

Harms

Pleural interventional procedures will only be performed as part of standard of care. Standard medical care and any drainage procedures (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the patient.

Adverse event reporting

All adverse events relating to the trial investigations, 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.

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 adverse events relating to the investigations occurring during the course of the clinical trial (i.e., from signing the informed consent until death or the end of the study follow up period, whichever comes first) will be collected and documented by the investigator 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 hospitalization by ≥24 h (i.e., unexpected overnight admission)
- is deemed serious for any other reason such that it is thought to jeopardize 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.

Auditing

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.

Confidentiality

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

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.

DISCUSSION

This is the first study to investigate bendopnoea in patients with pleural effusion. It is designed to have an unselected cohort, with few exclusion criteria to ensure that the results are generalisable. The presence and clinical significance of bendopnoea at baseline (i.e., pre-pleural fluid drainage) in the context of pleural effusion requires thorough investigation. The post-drainage assessment of patients will provide insight into whether the presence of bendopnoea is able to predict clinical outcomes. The findings of this study may enhance our understanding of pleural effusion related dyspnoea, which is currently limited.

Trial status at submission

Protocol version: Version 1.00/05.02.2022

Date recruitment began: 31.08.2022 Estimated recruitment completion date: 31.12.2024

Dissemination policy

Results from this study will be published in peer-reviewed journals and presented at national and international conferences. Authorship eligibility guidelines will be discussed prior to publication.

AUTHOR CONTRIBUTIONS

Conceptualisation: BR, CJP-M, YCGL. *Funding acquisition*: BR, YCGL. *Methodology*: BR, YCGL, CJP-M. *Project administration*: ALT, BR, BMI. *Data collection/enrolment*: BR, BMI, MD, MI, YCGL. *Data curation*: BR, BMI. *Formal analysis*: BR, BMI, YCGL; resources: YCGL. Supervision: CJP-M, YCGL. *Protocol preparation (original draft)*: BR, YCGL. All authors reviewed and approved final submission.

ACKNOWLEDGMENTS

The design of this trial incorporated input and feedback from the Pleural Consumer Reference Group. Open access publishing facilitated by Edith Cowan University, as part of the Wiley - Edith Cowan University agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

This study has received funding from the Sir Charles Gairdner Research Advisory Council research project grant. The study is sponsored by the Institute for Respiratory Health, a not-for-profit organization. The funder is not involved in the planning of the study, gathering, analysing, and interpreting the data, or in preparing the manuscript.

CONFLICT OF INTEREST STATEMENT

Prof Y. C. Gary Lee is an Editorial Board member of Respirology Case Reports and a co-author of this article. He was

excluded from all editorial decision-making related to the acceptance of this article for publication. The other authors have no conflict of interests to report.

DATA AVAILABILITY STATEMENT

Investigators at the lead site will have access to the final trial dataset. Supporting data including standard operating procedures, details of data management procedures, case report forms, and datasets generated and/or analysed during the current study will be available to the scientific community with as few restrictions as possible, while retaining exclusive use until publications of major outcomes. Data requests from qualified researchers should be made to YCGL (gary.lee@uwa.edu.au).

ETHICS STATEMENT

Sir Charles Gairdner and Osborne Park Health Care Group Human Research Ethics Committee has approved the study (RGS0000004786). Results will be published in peer-reviewed journals and presented at scientific conferences. Study investigators will ensure that any amendments to the protocol is approved by the ethics committee and signed by any patients subsequently entering into the trial and those currently in the study, if affected by the amendment.

ORCID

Bianca M. Iacopetta https://orcid.org/0009-0003-7510-5261
Y. C. Gary Lee https://orcid.org/0000-0002-0036-511X

REFERENCES

1. Muruganandan S, Azzopardi M, Thomas R, Fitzgerald DB, Kuok YJ, Cheah HM, et al. The pleural effusion and symptom evaluation (PLEASE) study of breathlessness in patients with a symptomatic pleural effusion. Eur Respir J. 2020;55(5):1900980.
2. Light RW, Lee YCG. Textbook of pleural diseases. 3rd ed. Boca Raton: CRC Press, Taylor & Francis Group; 2016.
3. Fysh ET, Smith NA, Lee YCG. Optimal chest drain size: the rise of the small-bore pleural catheter. Semin Respir Crit Care Med. 2010;31(6):760–8.
4. Hooper CE, Welham SA, Maskell NA. Pleural procedures and patient safety: a national BTS audit of practice. Thorax. 2015;70(2):189–91.
5. Thomas R, Jenkins S, Eastwood PR, Lee YCG, Singh B. Physiology of breathlessness associated with pleural effusions. Curr Opin Pulm Med. 2015;21(4):338–45.
6. Baeza-Trinidad R, Mosquera-Lozano JD, El Bikri L. Assessment of bendopnea impact on decompensated heart failure. Eur J Heart Fail. 2017;19(1):111–5.
7. Thibodeau JT, Turer AT, Gualano SK, Ayers CR, Velez-Martinez M, Mishkin JD, et al. Characterization of a novel symptom of advanced heart failure: bendopnea. JACC Heart Fail. 2014;2(1):24–31.
8. Karauzum K, Karauzum I, Sahin K, Baydemir C, Baris Argun S, et al. Bendopnea and its clinical importance in outpatient patients with pulmonary arterial hypertension. Acta Cardiol Sin. 2018;34(6):518–25.
9. Pranata R, Yonas E, Chintya V, Alkatiri AA, Siswanto BB. Clinical significance of bendopnea in heart failure-systematic review and meta-analysis. Indian Heart J. 2019;71(3):277–83.
10. Falk RH. 'Bendopnea' or 'kamptopnea?': some thoughts on terminology and mechanisms. JACC Heart Fail. 2014;2(4):425.
11. Martínez Cerón DM, Garcia Rosa ML, Lagoeiro Jorge AJ, De Andrade Martins W, Tinoco Mesquita E, Di Calafriori Freire M, et al. Association of types of dyspnea including 'bendopnea' with cardiopulmonary disease in primary care. Rev Port Cardiol. 2017;36(3):179–86.
12. Babb TG, Wyrick BL, DeLorey DS, Chase PJ, Feng MY. Fat distribution and end-expiratory lung volume in lean and obese men and women. Chest. 2008;134(4):704–11.
13. Mishra EK, Corocoran JP, Hallifax RJ, Stradling J, Maskell NA, Rahman NM. Defining the minimal important difference for the visual analogue scale assessing dyspnea in patients with malignant pleural effusions. PLoS One. 2015;10(4):e0123798.
14. Davies HE, Mishra EK, Kahan BC, Wrightson JM, Stanton AE, Guhan A, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. JAMA. 2012;307(22):2383–9.
15. Mishra EK, Clive AO, Wills GH, Davies HE, Stantan AE, Al-Aloul M, et al. Randomized controlled trial of Urokinase versus placebo for nondraining malignant pleural effusion. Am J Respir Crit Care Med. 2018;197(4):502–8.
16. Thomas R, Fysh ETH, Smith NA, Lee P, Kwan BCH, Yap E, et al. Effect of an indwelling pleural catheter vs talc pleurodesis on hospitalization days in patients with malignant pleural effusion: the AMPLE randomized clinical trial. JAMA. 2017;318(19):1903–12.
17. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med. 2002;166(1):111–7.
18. Solway S, Brooks D, Lacasse Y, Thomas S. A qualitative systematic overview of the measurement properties of functional walk tests used in the cardiorespiratory domain. Chest. 2001;119(1):256–70.
19. Knox AJ, Morrison JF, Muers MF. Reproducibility of walking test results in chronic obstructive airways disease. Thorax. 1988;43(5):388–92.
20. Peddle-McIntyre CJ, Bell G, Fenton D, McCargar L, Courneya KS. Feasibility and preliminary efficacy of progressive resistance exercise training in lung cancer survivors. Lung Cancer. 2012;75(1):126–32.
21. Graham BL, Steenbruggen I, Miller MR, Barjaktarvic IZ, Cooper BG, Hall GL, et al. Standardization of spirometry 2019 update. An official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70–88.
22. Light RW, Rogers JT, Cheng D, Rodrigeuz RM. Large pleural effusions occurring after coronary artery bypass grafting. Cardiovascular surgery associates, PC. Ann Intern Med. 1999;130(11):891–6.
23. Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. Muscle Nerve. 2013;47(3):319–29.
24. Epelman M, Navarro OM, Daneman A, Miller SF. M-mode sonography of diaphragmatic motion: description of technique and experience in 278 pediatric patients. Pediatr Radiol. 2005;35(7):661–7.
25. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods, reproducibility, and normal values. Chest. 2009;135(2):391–400.

How to cite this article: Roy B, Iacopetta BM, Peddle-McInytre CJ, Donaghy M, Ing M, Tan AL, et al. The third PLeural Effusion And Symptom Evaluation (PLEASE-3) study: Bendopnoea in patients with pleural effusion. Respirology Case Reports. 2024;12(6):e01410. https://doi.org/10.1002/rcr2.1410