It is a requirement of Good Clinical Practice (GCP) and the Research Governance Framework for Health & Social Care 2017, that all research projects have a scientifically sound and ethically valid protocol.

The protocol is the starting point of any high quality research and all research studies must be conducted according to the protocol. A protocol provides written evidence for the necessity and feasibility of a study, as well as giving a detailed plan of investigation.

This document is to be submitted for approval to a Research Ethics Committee (REC). This allows the ethical and peer review processes to validate the scientific and ethical considerations of the study. The guidance detailed below is for Clinical Trials of Non Investigational Medicinal Products (Non CTIMPs).

TITLE OF THE PROTOCOL: A randomised controlled trial to evaluate the impact of thoracic **PR**ehabilitation with **I**nspiratory **M**uscle t**R**aining c**O**mpared to **S**tandard pr**E**habilitation in surgical lung cancer patients.

Short title/Acronym: PRIMROSE Trial

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STUDY SUMMARY/SYNOPSIS

TITLE	A randomised controlled trial to evaluate the impact of thoracic PRehabilitation with Inspiratory Muscle tRaining cOmpared to Standard prEhabilitation in surgical lung cancer patients.
SHORT TITLE	**PRIMROSE** Trial
Protocol Version Number and Date	Standard Protocol Version Number 3.5 and date 03/02/25
Methodology	Type of study: randomised control trial
Study Duration	Two years
Study Centre	Cardiothoracic centre, Morriston Hospital
Objectives	To compare inspiratory muscle training (IMT) with standard Prehabilitation (Prehab) to Prehab alone, in lung cancer patients for surgery.
Number of Subjects/Patients	One hundred and thirty-four patients will be recruited for the study (67 for each arm) and with an anticipated attrition rate of 20-25%, one hundred patients will finally be studied.
Main Inclusion Criteria	All adult lung cancer patients > 18 years diagnosed or suspected of non-small cell lung cancer (NSCLC) with surgically resectable disease, who are referred for pre-treatment optimization with Prehab from the lung cancer Multi-Disciplinary Teams (MDTs) across South West Wales (Swansea lung MDTs, the Hywel Dda lung MDTs and Princess of Wales lung MDT). Lung cancer patient are referred for pre-treatment optimization with Prehab if they meet the following referral criteria: ≥1 Medical Research Council (MRC) dyspnoea score; or ≥1 World Health Organization (WHO)

	performance status (PS); age ≥ 70 years or frailty index >3; borderline or poor pulmonary function (forced expiratory volume in one second (FEV1) or diffusion capacity for carbon monoxide (DLCO) <50%); sedentary patients despite having adequate FEV1 or DLCO. Patients will be included in the trial if they are capable of giving consent to participation and aged 18 and over. Additionally, patients who have no contraindications to IMT use.
Statistical Methodology and Analysis	Our aim is to evaluate the impact of thoracic Prehab with IMT compared to standard Prehab in reducing post operative pulmonary complications following surgical resection in lung cancer patients in a RCT. Descriptive statistics will be used to summarise participants' characteristics and outcome measures. Statistical analyses will be performed using SPSS statistical software, version 20.0 (IBM Corporation, Armonk, NY, USA). Two-sided significance tests will be used (a\0.05). Data will be presented as mean and standard deviation (SD), or median and interquartile range (IQR) for variables with a skewed distribution. Differences between groups in categorical variables will be tested with Chi square or Fisher's exact test. For continuous data the student's t test or the Mann–Whitney U test will be used. The Wilcoxon signed rank test will be used to compare MIP and QoL at T0 and T1 and T2. Relative risk will be calculated for post operative pulmonary complications (PPCs) graded 1-V using the Clavien Dindo classification and impact of IMT on the study group compared to the control group. Assuming a 36.7 incidence of PPC after surgery in the control arm and using a significance level of 0.05 and a power of 80%, 50 patients are required in each arm.

Protocol Agreement Page

The clinical study as detailed within this research protocol **(Version 3.7, dated 05/06/25)**, or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

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Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
BACPR	British Association for Cardiovascular Prevention and Rehabilitation
CA	Competent Authority
CI	Chief Investigator
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
CRO	Contract Research Organisation
DLCO	Diffusion capacity for carbon monoxide
DMC	Data Monitoring Committee
EC	European Commission
EORTC	European Organization for Research and Treatment of Cancer
FEV1	Forced expiratory volume in one second
FITT	Frequency, Intensity, Type and Time principles of training
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Research Practice
HLOS	Hospital length of stay
HRQol	Health related quality of life
IASLC	International Association for the Study of Lung Cancer
ICF	Informed Consent Form
IQR	Interquartile range
IMT	Inspiratory muscle trainer
IS	Incentive spirometry
IP	Intellectual Property
ISRCTN	International Standard Randomised Controlled Trial Number
LHC	Lung Health Check
LOA	Levels of activity
LOHS	Length of hospital stay
MDT	Multi-Disciplinary team
MIP	Maximal Inspiratory Pressure
MRC	Medical Research Council dyspnoea score
Main REC	Main Research Ethics Committee

NHS	National Health Service
NHS R&D	National Health Service Research & Development
NICE	National Institute for Health and Care Excellence
NSCLC	Non-small cell lung cancer
PI	Principle Investigator
PIS	Patient Information Sheet
PPI	Patient and public involvement representatives
PPC	Post-operative pulmonary complication
Prehab	Thoracic Prehab Programme
PREM	Patient reported experience measure
PROM	Patient reported outcome measure
PS	World Health Organization Performance Status
QA	Quality Assurance
QALY	Quality adjusted life years
QC	Quality Control
QOL	Quality of life
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
SBUHB	Swansea Bay University Health Board
SCTC	Society of Cardiothoracic Surgery
SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TMG	Trial Management Group
TSC	Trial Steering Committee
UK	United Kingdom
WHO	World Health Organization
6MWT	6 minute walk test

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1. Introduction

1.1. Background

Lung cancer is the most common cause of cancer-related deaths in Wales (1). Although surgical resection for early-stage lung cancer with curative intent remains the primary treatment, patients with significant smoking related underlying cardiopulmonary disease and impaired pulmonary function, dyspnoea, frailty and decreased activity levels are unfit for surgery and referred for alternative treatment (2,3). Secondly, individuals who proceed to lung resection, thoracic surgery and general anaesthesia may have direct effects on their respiratory system potentially leading to postoperative pulmonary complications (PPCs), which increases hospital morbidity, prolongs hospital length of stay (HLOS) impacts on the quality of life (QOL) of patients and adds to health-care costs (4). Our aim is to evaluate whether incorporating a breathing training device, POWERBreathe into the existing standardised thoracic prehabilitation program (Prehab) will optimise unfit patients physically for surgery, and following surgery reduce their risk of developing PPC's, reduce HLOS and improve QOL of patients and improve service outcomes (5).

The PRIMROSE study aims to compare two groups of patients referred for Prehab who have lung cancer treatable with surgery: (A) standard Prehab and training with the inspiratory muscle training (IMT) device; and (B) standard Prehab alone, in non-small cell lung cancer patients (NSCLC) undergoing lung resection surgery, with clear primary and secondary outcome measures.

One hundred and thirty-four patients will be recruited for the study (67 for each arm) and with an anticipated attrition rate of 25%, one hundred patients will finally be studied (6,7). With 134 recruited and an attrition rate of 25%, only 100 will remain (50 in each arm). The primary outcome measure tested will be the proportion of patients in each group experiencing postoperative pulmonary complications (PPC), which will be graded I-V using the Clavien Dindo Classification (8). PPCs will be broadly classified as minor (grade 1) and major complications (grade 2-5 where 5 is death). What we want to learn from this RCT study is whether IMT helps reduce grade ≥2 PPCs to either grade 1 or no complications and thereby help shorten the length of stay in hospital for patients undergoing lung resection surgery.

Secondary outcome measures tested will be Medical Research Council (MRC) dyspnoea score, World Health Organization (WHO) performance status (PS), levels of activity (LOA),

thoracoscore, frailty index (FI), six-minute walk distance test distance (6MWD), maximum inspiratory pressure (MIP) and quality of life (QoL) data using the EORTC QLQ-30 questionnaire (9). In addition, researchers will collect safety data on, complication rates, mortality and HLOS. The quality of Prehab delivery and outcomes will be closely monitored in accordance with good clinical practice in research guidelines.

1.2. Preclinical Data

Lung cancer treatment has complex and critical challenges as highlighted by The Welsh NHS Confederation (2015), the Welsh Government Parliamentary Review of Health and Social Care in Wales (2018) and A Healthier Wales (2018) (10,12). These include shifting demographics, an ever-ageing population and increased prevalence of complex and chronic conditions alongside fiscal constraints. For example, 63% of patients with lung cancer have chronic obstructive pulmonary disease (COPD), resulting in breathlessness and poor exercise tolerance and predispose surgical patients to post-operative pulmonary complications (PPC's) increased morbidity, longer hospital length of stays (HLOS) and mortality (4,13)

Smoking accounts for about 90% of all lung cancer cases (13). Patients with resectable NSCLC may have smoking related underlying cardiopulmonary disease causing significant dyspnoea (due to impaired or poor pulmonary function), impaired performance status (PS) and impaired levels of activity (LOA) (14,15). Loss of lung tissue in deconditioned NSCLC patients may grossly impair their postoperative ventilatory function, predisposing them to significant dyspnoea and cardiopulmonary complications. These patients are considered high-risk for surgery or inoperable and referred for radiotherapy, systemic anticancer treatment, or palliative care instead (2-4, 13-15). In Wales, an average of only 17% of patients undergo lung resection annually (16).

Of those individuals who proceed to lung resection, thoracic surgery and general anaesthesia may have direct effects on their respiratory system predisposing patients to PPCs, which increases hospital morbidity, prolongs HLOS and adds to health-care costs (4). PPCs in patients for thoracotomy and lung resection with chronic lung disease have been reported to be as high as 30% (4). Decreased lung expansion due to poor inspiratory muscle strength (respiratory muscle weakness) causes atelectasis and PPCs (4)). Reduced respiratory muscle function along with reduced mucociliary function and bacterial proliferation promote colonisation of the respiratory tract by bacteria leading to pneumonia and acute respiratory distress syndrome with patients requiring intensive care treatment and longer HLOS, which

increase National Health Service (NHS) costs, places pressures on critical care beds and increases mortality (4).

Annually published lung cancer audit data for Wales consistently demonstrates a wide variation in the number of NSCLC patients receiving surgery with curative intent across the eight lung cancer Multi-Disciplinary Teams (MDT's) across South Wales (16). Fitness for surgery and area of deprivation of patients play a major role in this variation. The Equality Act (2010) advocates equality of opportunity. The SBUHB Prehab service, ensures that male and female patients, elderly patients and patients with diverse backgrounds are given the same opportunities to access high quality of surgical care and support. Hence, our proposed research project aims to ensure that vulnerable, high-risk, unfit NSCLC patients with surgically resectable disease are not denied curative surgery and instead will benefit by receiving surgery. Furthermore, to ensure equity in provision of surgical care to patients requiring thoracic surgery, the Welsh Government aims to establish a South Wales Adult Thoracic Surgical Service based at Morriston Hospital, Swansea by 2027. The aim of our SBUHB Prehab service is to ensure that there is equity in the provision of a standardised, evidence based Prehab service to all patients across South Wales especially when referrals from all South Wales Health Board lung MDTs commence to the thoracic SBUHB Prehab service by 2027 (Figure 1).

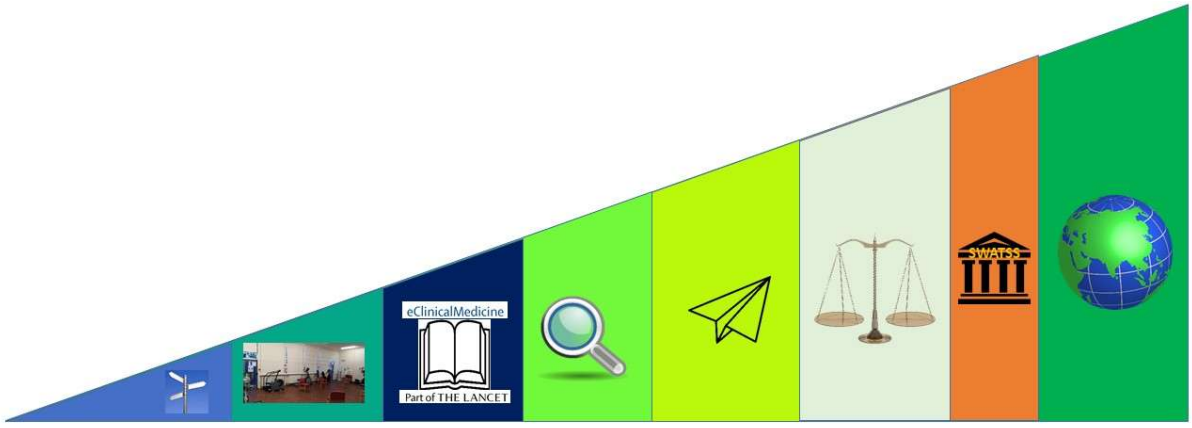

Figure 1. Impact and anticipated future progression

SWATSS = South Wales Adult Thoracic Surgical Service; WHSSC = Welsh Health Specialised Services Committee

1.3. Clinical Data

Analysis of our prospective data, which was published in the Lancet journal EClinicalMedicine, suggests that patients with dyspnoea, impaired PS, decreased LOA, frailty, and borderline or poor lung function can be optimized with a standardized Prehab program, allowing them to undergo curative lung surgery safely with acceptable frequency of PPC's, LOHS and mortality (15). Despite optimisation, there remain a section of patients who remain unfit for surgery or following surgery develop complications and experience longer stays in the high dependency unit and hospital (15).

There is emerging evidence that adding a hand-held Inspiratory Muscle Training (IMT) device (Figure 2) to Prehab further optimises surgical patients and improves post-surgical outcomes by reducing PPCs which results in shorter HLOS and reduces mortality (17-20). IMT improves the strength and endurance of inspiratory muscles, namely the diaphragm and intercostal muscles through a series of breathing exercises and greatly improves the ability of individuals to take in deep breaths following surgery and expectorate and clear their airway of retained secretions more effectively, which helps reduce PPCs (17-20). IMT is analogous to strengthening one's respiratory muscles with weightlifting and inspiratory muscles are able to work for longer duration (17-20). For this study we plan to use the POWERbreathe Medic IMT device which does have a CE mark. The device is not being used outside of the purposes for which it is CE marked for this research study. The POWERbreathe medic IMT device is evidence based for a variety of medical conditions such as chronic lung disease and thoracic surgery, and is currently used by multiple patient groups, including pre operative cardiac patients as part of routine care in the Health Board. The POWERbreathe medic IMT is a single patient use device that is not decontaminated and passed onto other patients to use after the study.

On the contrary, following lung resection, to manage pleural space complications of air leak, effusion and empyema, RCT-level evidence suggests that temporarily paralysing the diaphragm (an inspiratory muscle responsible for almost 80% of inspiratory effort) with cryo-neuro-ablation of the phrenic nerve, does not significantly prolong HLOS, PPCs and mortality (21).

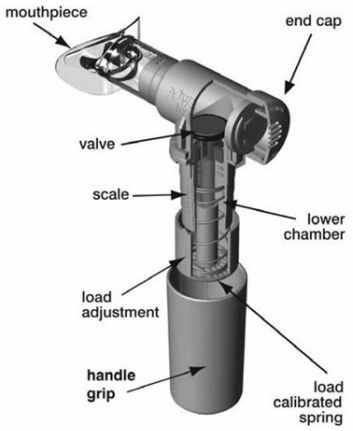

Figure 2. POWERBreathe Inspiratory Muscle Training Device

In the presence of suggested equipoise, to obtain high level evidence for introducing IMT with Prehab into clinical practice for NSCLC surgical patients, we searched the Medline, Embase and the Cochrane library databases for English language RCTs, systematic reviews and meta-analyses published on “pulmonary rehabilitation” between Jan 1946 to May 2022 for “inspiratory muscle training”, “POWERbreathe Medic”, “inspiratory spirometry” (IS), “surgery”. Our search revealed 181 publications. 4 publications met the search question comparing IMT with Prehab and IS. Two RCTs were in cardiac surgery, one ‘pilot’ in upper gastro-intestinal surgery and one ‘pilot’ RCT in lung cancer surgery (Figure 3) (22-25).

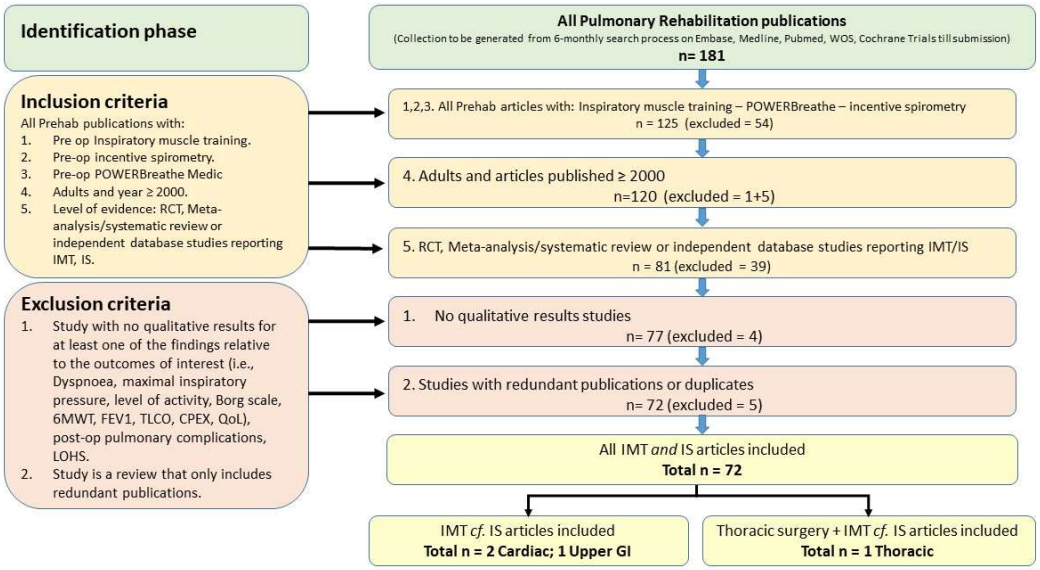

Figure 3. PRISMA flow diagram for a Systematic Review of Inspiratory Muscle Training (IMT) vs Standard Prehab

The four RCTs, including the pilot RCT in lung cancer surgery, did not describe the impact of IMT on the quality of life (QoL) of patients who underwent surgery (22-25).

Whilst the four RCTs suggested that incorporating an IMT device to strengthen the diaphragm and muscles of inspiration improved pulmonary function prior to surgery, and following surgery reduced PPCs and HLOS, RCT level evidence evaluating the effectiveness of IMT in NSCLC surgical patients was graded low as the pilot RCT was underpowered (22) (12 patients in IMT group and 9 patients control group).

Lung resection patients commonly have COPD, reduced respiratory function, obesity, are on bronchodilators and develop PPCs. The RCT in cardiac surgical patients however, excluded these patients who are more likely to develop PPCs. Unlike abdominal and cardiac surgery, in lung cancer surgery a large volume of lung tissue is removed, which further compromises pulmonary function predisposing patients to increased PPCs, mortality, HLOS and impacts QoL. As cardiac and abdominal surgical patients do not reflect the thoracic surgical population as lung tissue is not removed at surgery in these patient populations. Hence, it is not possible to extrapolate their RCT evidence to lung resection patients (21-25)

Additionally, there is significant research with IMT in the intensive care population (26), however these results cannot be generalised to our population of patients for lung resection surgery. Whilst there are similarities between the two patient groups, such as chronic respiratory conditions and deconditioning, patients can suffer other intensive care related conditions such as critical illness polyneuropathy from sepsis. Additionally, outcome measures between the two patient populations differ.

1.4. Rationale and Risks/Benefits

We hypothesise that prior to surgery, an IMT device in combination with a standard Prehab program compared with Prehab alone, will further improve the strength and endurance of the surgical NSCLC patients' inspiratory muscles used for breathing. By doing so, IMT with Prehab will allow patients who have undergone lung resection surgery to clear their airway of secretions more effectively in the post-operative period and provide a significant benefit to patients by lowering their risk of developing PPCs and shorten their HLOS after surgery, improve their overall QoL and additionally reduce NHS costs.

There are no expected risks to participants of this trial. Our previous studies, have shown that thoracic Prehab safely optimises patients for surgery (14,15). Good tolerance with IMT devices have been reported, although can cause feelings of fatigue (27,28).

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2. Objectives and Design

2.1. Trial Objectives

Primary Objective: A randomised controlled trial to evaluate the impact of thoracic **PR**ehabilitation with **I**nspiratory **M**uscle t**R**aining c**O**mpared to **S**tandard pr**E**habilitation in surgical lung cancer patients [PRIMROSE Trial].

Recruitment rate: The study aims to recruit 134 patients for randomisation over twelve months, with 67 randomised to the intervention group and 67 to the control group (6).

Retention rate: These are high-risk patients and a high attrition rate in this population is considered normal**.** We anticipate the retention of 50 patients in each arm following 1:1 randomisation, and is based on our previous study (15), which showed that following assessment, 6.8% NSCLC patients fail to attend Prehab and 1.1% died prior to commencing Prehab. Likewise, following Prehab, 75.8% patients are ready to proceed with surgery. The attrition rate is an estimate and is anticipated attrition to be 20%-25%.

Secondary Objectives:

Adherence to trial procedures: It is anticipated that 80% of participants will adhere to the study protocol.

Collection of participant outcome data and completion rate: It is anticipated that all data on each of the individual participants at each time point in each arm of the study will be accurately and contemporaneously collected by the research team. The percentage of patients in whom all data sets at each time point is accurately and contemporaneously obtained will describe the data completion rate, which is an anticipated >95%.

Follow-up: Following surgery, >80% are expected to successfully complete the post-discharge assessments. We anticipate a >80% follow-up assessment.

2.2. Trial Design:

This is a randomised controlled PRIMROSE trial. This trial will be single centred, as there are very few centres in the United Kingdom (UK) that deliver this highly specialised service.

Study population: Lung cancer patients with surgically resectable disease referred for pre-treatment optimization with Prehab, from the lung cancer Multi-Disciplinary Teams (MDT's) across South West Wales. Eligible patients will be randomised to the trial on a 1:1 ratio to either the intervention arm or control arm [figure 4].

Participants in group A will receive standard Prehab and training with the IMT device (POWERBreathe); participants in group B will receive standard Prehab alone.

2.3. Figure 4. Study Scheme Diagram:

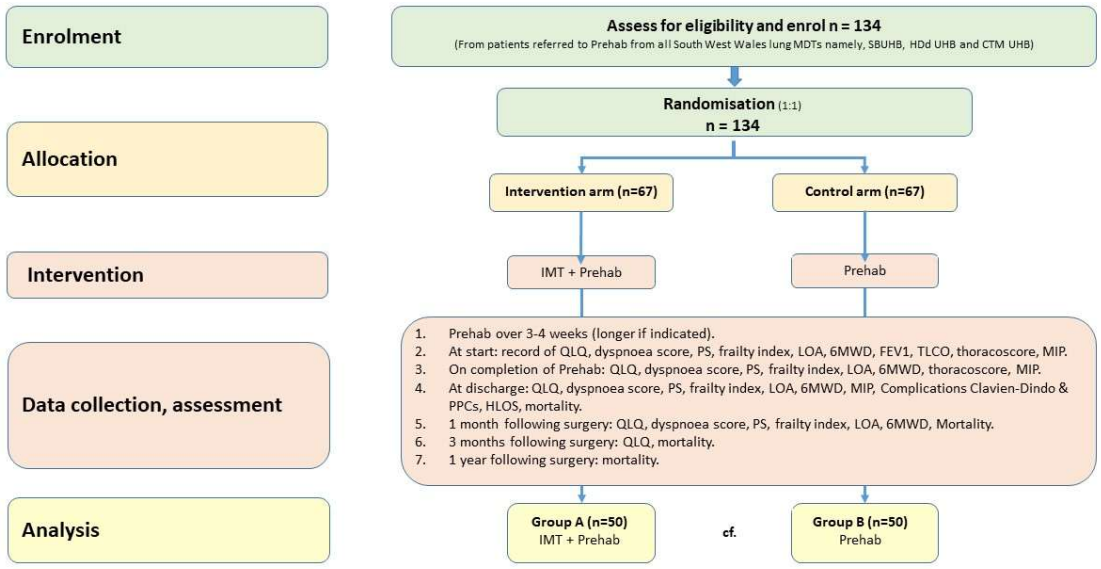

Figure 4. Consolidated standards of reporting trials (CONSORT) diagram for the PRIMROSE Trial

6MWD= 6 minute walk distance test; cf. = compared with; CTM UHB = Cwm Taf University Health Board: FEV1= Forced expiratory volume in 1 second; ; HDd = Hywel Dda Health Board; IMT= Inspiratory muscle training; LOA = level of activity; HLOS = Hospital length of stay; PPCs = post-operative pulmonary complications; PS= performance status: TLCO= transfer factor; QLQ= quality of life questionnaire;

To ensure the effectiveness of our study protocol, we have utilised the principles of the UK Medical Research Council guidance framework for developing and evaluating complex interventions pilot and feasibility studies (6,7).

2.4. Statistical Methodology and Analysis

2.4.1. Sample size, justification and calculations

Our literature search did not bring up a suitable RCTs on the use of POWERBreathe Inspiratory Muscle Trainer (IMT) in lung resection patients. Hence, we used the outcome data from the RCT on cardiac patients on whom POWERBreathe IMT was used and we have experience with. We acknowledge that the cardiac surgery patient population are very different and do not accurately reflect our study population (as patients undergoing cardiac surgery do not undergo lung resection). There is one RCT on the use of inspiratory spirometry used in patients undergoing lung resection in order to strengthen their diaphragm function prior to surgery (29). Inspiratory muscle training using inspiratory spirometry is different to the POWERBreathe IMT. However, the patient population and design of this RCT are more in line with our PRIMROSE Trial, making it more pertinent to use the data from this RCT instead of the RCT in a cardiac population. Hence, using the data from the lung resection patient trial, and assuming a 36.7% incidence of PPC after surgery in the control arm and using a significance level of 0.05 and a power of 80%, the online calculator estimates 50 patients are required in each arm of the study (Figure 5).

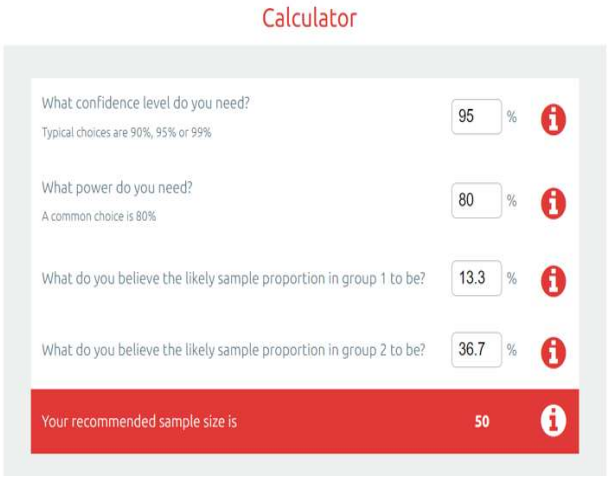

Figure 5: Online calculator to estimate sample size (29).

This sample size is realistic as Prehab receives on an average of 127 annual patient referrals per year.

Data collection

QoL data using EORTC QLQ-30 questionnaire will be collected at initial assessment (T0) and on completion of Prehab (T1) as final assessment, then post-surgery at discharge (T2) and at 1 month following surgery (T3).

Subjective outcome measures data include dyspnoea score, PS, thoracoscore, frailty index (FI), LOA and objective measures include 6-minute walk distance test (6MWD) at initial assessment (T0), after every two weeks in Prehab to assess for improvement, and finally at final assessment prior to participants proceeding to surgery (T1) (14,15,30). LOA, measured using the Borg scale of perceived exertion, will be recorded as sedentary, moderately active or active and supplemented by the 6MWD. The 6MWD will be performed using a 10m corridor instead of 30m (31). A 10 metre track along a flat corridor, will be used to measure the distance walked in metres within the 6 minutes. A 10m track was used in our previously published study and proved very effective. The American Thoracic Society guidelines state a distance of 30 metres (100 foot) should be used, however this is difficult practically. It is rare to find a 30-metre corridor in a hospital that is quiet and can allow a chair to be positioned for seated rests. A 10 metre track will be better from a health and safety point of view, as well as giving patient's privacy to focus on the self-paced walk test. These above outcome measures are already standard care for all Prehab patients (14,15).

Calculating the thoracoscore for each individual for lung resection in percentage describes the mortality risk of the individual for surgery. This is already standard operating procedure (SOP) for obtaining informed consent for lung resection surgery, and will be calculated for each participant (T0 and T1) (2,32).

The maximal inspiratory pressure (MIP) for both groups will be measured using a POWERbreathe device (Figure 2) at initial assessment (T0), on completion of Prehab (T1) and at discharge (T2). Measuring MIP is not standard practice for Prehab and will be an additional and essential outcome measure. It is required to assess the progress of each individuals improvement with the Prehab. Due consideration regarding IMT contraindications in patients to avoid harm or adverse events is included in our inclusion/exclusion criteria.

Following surgery, data on PPC's and HLOS will be collected by the researcher. This is standard practice for the prehab service.

Post-discharge assessment: Our primary objective is to determine whether IMT prior to surgery with Prehab helps reduce PPC following surgery, which is up to the point of discharge from hospital (alive or dead). This is one time point. Hence, it is anticipated that all patients will complete the discharge assessment for complications. Thus, the study is not underpowered for the primary end point.

Mortality rates will be collected at discharge, 1 month, 3 months, and 365 days post-surgery.

2.4.2 Analysis Plan

Our aim is to evaluate the impact of thoracic Prehab with IMT compared to standard Prehab in reducing post operative pulmonary complications following surgical resection in lung cancer patients in a RCT.

The analysis will include descriptive data (means and standard deviation) on all outcomes collected, including levels of missing data, leading to the calculation of clinically important differences. Descriptive statistics will be used to summarise participants' baseline characteristics and outcome measures.

Statistical analyses will be performed using SPSS statistical software, version 20.0 (IBM Corporation, Armonk, NY, USA). Two-sided significance tests will be used (a\0.05). Data will be presented as mean and standard deviation (SD), or median and interquartile range (IQR) for variables with a skewed distribution. Differences between groups in categorical variables will be tested with Chi square or Fisher's exact test. For continuous data the student's t test or the Mann–Whitney U test will be used. The Wilcoxon signed rank test will be used to compare MIP and QoL at T0 and T1 and T3. Relative risk will be calculated for post operative pulmonary complications (PPCs) graded 1-V using the Clavien Dindo classification and impact of IMT on the study group compared to the control group. Assuming a 36.7% incidence of PPC after surgery in the control arm and using a significance level of 0.05 and a power of 80%, 50 patients are required in each arm of the study for analysis."

2.4.3. Project statistician / methods expert

Statistical analyses will be performed using SPSS statistical software, version 20.0 (IBM Corporation, Armonk, NY, USA) by the chief investigator who is familiar with the use of this software and has previously published data in the lancet journals eclinical medicine (15).

3. Subject Selection

3.1. Number of subjects and subject Selection

Daily screening of new prehab referrals by the principal investigator or research team, using a consecutive sample approach will be used for participant recruitment. This means selecting all patients who meet the eligibility criteria. Patients over a 12-month period (from January 2025) will be approached to gain consent. However, if recruitment numbers are an issue the study will be extended by six months.

3.2. Inclusion Criteria:

Lung cancer patients with surgically resectable disease who are referred for pre-treatment optimization with Prehab from the lung cancer Multi-Disciplinary Teams (MDTs). The referral criteria for Prehab is one or more of the following (15):

- ≥1 Medical Research Council (MRC) dyspnoea score
- ≥1 World Health Organization (WHO) performance status (PS)
- Age ≥ 70 years
- Frailty index >3
- Borderline or poor pulmonary function (forced expiratory volume in one second (FEV1) < 50% or diffusion capacity for carbon monoxide (DLCO) <50%)
- Sedentary patients despite having adequate FEV1 or DLCO

Additionally:

- Surgical resection can be performed, including endobronchial excision of tumour, or lobectomy, segmental resection, pneumonectomy or wedge resection, either via a minimally invasive approach or a standard thoracotomy approach
- Patients will be included in the trial if they are capable of providing verbal written consent for Prehab, and written consent for undergoing surgical resection for lung cancer
- Are over 18 years of age
- All patients will be considered regardless of their baseline respiratory muscle strength

3.3. Exclusion Criteria:

- Inclusion criteria not met
- Patients who have undergone recent abdominal surgery and those with an abdominal hernia
- Patients diagnosed with other cancers namely, patients with metastatic lung cancer, mesothelioma, sarcoma, mediastinal tumours, or benign diseases
- Patients who decline Prehab
- Patients who do not consent to Prehab, do not attend or have died prior to commencing Prehab. Patients who do not consent to surgery.
- Patients with a high cardiovascular risk for Prehab and awaiting investigations or interventions (including unstable angina and syncope)
- Patients with a serious concomitant disorder that would compromise patient safety during Prehab
- Patients with a history of spontaneous pneumothorax and/or evidence of large bullae on radiological imaging
- Patients who have suffered from or likely to suffer from costochondritis
- Patients with marked osteoporosis with history of rib fractures
- Patients with pulmonary hypertension
- Patient with a perforated ear drum
- If a participant is involved in a study similar, with potential to cause bias or conflict of interest then they will be excluded
- Patients with worsening heart failure signs and symptoms after IMT

To prevent the transmission of respiratory infections, the research team will advise patients not to share the device with family members. If patients are suffering from a cold, sinusitis or respiratory tract infection they will be advised not to use the device until their symptoms have resolved.

Participants who do not understand written and/or spoken English can access a translator through the health board.

The research team will collect a list of patients that decline to participate in the trial, to assess recruitment rates at the end of the study.

3.4. Criteria for Premature Withdrawal

Participants will be withdrawn from the study for the following reasons:

- Participants are no longer considered suitable for surgical lung resection by the MDT. Other treatment options may be considered more prudent such as radiotherapy or systematic anticancer treatment or best supportive care.
- The participant decides they no longer wish to be part of the study or have decided against surgical resection
- The research team decide it is unsafe for the participant to continue due to medical, safety and regulatory concerns. This includes adverse cardio-respiratory events relating to the patients physical conditioning as assessed by the cardiothoracic physiotherapists
- If the participant becomes lost to follow-up as deemed by the research team
- If the participant loses their capacity during the study period (including death)
- A significant increase in post-surgical mortality

Patients have the right to refuse study participation.

If a participant loses capacity to consent or withdraws consent, they will be withdrawn from the study. Identifiable data already collected with consent would be retained and used in the study. No further data would be collected or any other research procedures carried out on or in relation to the participant.

4. Study Procedures

4.1. Informed Consent Procedures

It is the responsibility of the research team, who have been appropriately trained cardiothoracic physiotherapists and technicians (as documented in the research delegation log) to obtain written informed consent from each subject prior to any study participation. The research team will be trained by the PI, on when to approach a potential participant, what information they should provide (written and verbally), and how to record details of the consent decision.

Informed Consent Forms (ICF) and Patient Information Sheets (PIS) will be available in large print, with clear written language and available in English and Welsh.

Additionally, the research team will provide adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

If a participant wishes to speak to a cardiothoracic surgeon, the research team will organize a telephone discussion. If necessary, a second consent visit should be arranged and the research team will not take consent at this time.

The patient should be given at least 24 hours to consider giving their consent for the study. If for any reason, less than 24 hours is given, the reasons should be documented, along with justification for this decision. The date that the PIS is given to the patient will be documented within the patient's notes to ensure that a minimum of 24 hours has been provided.

The PI or other member of the research team will explain to the potential participant that they are free to refuse any involvement within the study or alternatively withdraw their consent at any point during the study and for any reason.

Once a patient has consented to take part in the trial research study a research label should be attached to their hospital case notes to indicate involvement.

All relevant research related documentation should be filed in the participants physiotherapy notes. This will consist of a copy of the ICF and PIS .Written records of each research event for example randomization, trial visits or follow up phone calls will be recorded within the physiotherapy notes.

If there is any further safety information, which may result in significant changes in the risk/benefit analysis, the PIS and ICF will be reviewed and updated accordingly. All subjects that are actively enrolled on the study will be informed of the updated information and given a revised copy of the PIS/ICF in order to confirm their wish to continue on the study.

The informed consent process will not cease once the ICF has been signed; the practice of giving information about the research project to participants will be an ongoing process at each contact. Ongoing verbal consent will be confirmed and documented as part of each research-contact by the research team.

4.2. Screening Procedures

For each patient referred to Prehab, the diagnosis and stage of lung cancer will be validated with the data documented on the Welsh Clinical Portal system by the CI and research team. This is standard practice in the staging and management of lung cancer. The International Association for the Study of Lung Cancer (IASLC) lung cancer staging system, 8th edition, will be used for pre-treatment clinical staging of patients with suspected or diagnosed lung cancer (33).

4.3. Randomisation Procedures (if applicable)

Participants will be randomised 1:1 to either the intervention or control group without stratification using an online randomisation service, 'Sealed Envelope' (www. sealedenvelope.com) (34).

4.4. Schedule of Treatment for each visit

On initial face-to-face assessment, conducted within 5 working days of receiving the referral for Prehab, the research team will provide participants with participant information sheet and informed consent form. Informed consent to participate will be obtained. Patients can bring carers to the face-to face assessment if they wish.

Control group: The control group will receive a standard Prehab protocol.

Standard Prehab protocol is described in our previous pragmatic study published in the lancet journals eclinical medicine (15). Prehab will be provided to participants over 2–4 weeks with supervised once weekly sessions ~~with supervised two weekly sessions~~ of 70 minutes each, along with exercises for patients to carry out at home. Three weeks is an anticipated average based on published data and urgency to proceed to surgery as cancer can grow and become inoperable by six weeks. This area is much debated in the Prehab literature. Our aim is to ensure as many patients benefit with Prehab followed by lung resection surgery as possible, with broader health benefits to patients and a positive impact on their quality of life. Our previous study showed that patients can be physically optimised safely in as little as two weeks (15). However, for patients who may be slower to respond there is scope in our program for a more prolonged course of Prehab if required.

Outcome measures will be collected every two weeks on the Prehab programme by the research team, which is standard practice. As patients become eligible, they will withdraw from Prehab and proceed to surgery once a surgical date is confirmed. Management of individuals deemed unfit for surgery will be discussed at the individuals' local lung cancer MDT for consideration of alternative treatment options namely, radiotherapy, systemic anti-cancer treatment or palliative care.

Respiratory muscle training and breathing exercises. Both groups will receive incentive spirometry devices pre operatively. Participants will be encouraged to practice and train with the spirometer device three times daily, so can use the spirometer effectively post operatively. This is standard care as spirometers aid lung volumes and removal of secretions post operatively.

Cardiovascular exercises: namely, stationary cycle ergometry and upper and lower limb resistance exercises will be performed, whilst monitoring the heart rate, blood pressure and oxygen saturations (15). The rate of perceived exertion (RPE) will be measured using the Borg breathlessness scale and used twice at every session to measure the intensity at which each patient is working and guide them to increase or decrease their effort as required.

Home Exercise Program (HEP): individualised home exercise programme includes daily walking plan and stair climbing exercise (15). Training enabling them to maintain activities of daily living following surgery. The HEP will be continued following discharge after surgery.

Health education and smoking cessation advice will be provided to all current smokers prior to surgery and support following surgery (15). Where necessary nicotine replacement therapy will be provided.

Intervention group: The intervention group will receive IMT in addition to a standard Prehab protocol (as above). An MIP in cmH20, obtained at or greater than 1.5 seconds will be recorded, and the highest MIP of 3 valid breaths will be used as baseline. The IMT pressure in cmH20 will be set initially at 40% of the patients MIP. Participants will be taught to use the device in an upright position and instructed to perform six sets of six breaths with the resting times between each set of breaths reducing from 60 seconds, to 45 seconds, to 30 seconds, to 15 seconds, to 5 seconds. IMT will be used twice-daily preoperatively in the intervention group and not post operatively. Training load intensity on the IMT will be

increased preoperatively by the patient according to the rate of perceived inspiratory effort, on a modified Borg scale.

4.5. Schedule of Assessment (in Diagrammatic Format)

Figure 6 describes the time points at which assessments and data will be collected.

Measure	Researcher or participant completing	At assessment (T0)	Every two weeks of Prehab	On Prehab Completion (T1)	At hospital discharge (T2)	1 month post-op (T3)	3 month post-op (T4)	1 year post-op (T5)
EORTC QLQ-C30	Participant	+	-	+	+	+	+	-
Dyspnoea score	Researcher	+	+	+	+	+	-	-
PS	Researcher	+	+	+	+	+	-	-
Thoracoscore	Researcher	+		+	-	-	-	-
Frailty index	Researcher	+	+	+	+	+	-	-
LOA	Researcher	+	+	+	+	+	-	-
Researcher	Researcher	+	+	+	+	+	-	-
MIP	Researcher	+	-	+	+	-	-	-
FEV1	Researcher	+	-	-	-	-	-	-
TLCO	Researcher	+	-	-	-	-	-	-
HLOS (days)	Researcher	-	-	-	+	-	-	-
Mortality	Researcher	-	-	-	+	+	+	+
Post-op complications	Researcher	-	-	-	+	-	-	-

Figure 6. Time points at which assessments will be carried out and data collected.

6MWD test= 6 minute walk test; EORTIC = European Organization for Research and Treatment of Cancer; FEV1= Forced expiratory volume in 1 second; MIP = Maximum inspiratory pressure; IMT= Inspiratory muscle training pressure; LOA = level of activity; HLOS = Hospital length of stay; PS= performance status: TLCO= transfer factor; QLQ-C30 = quality of life questionnaire.

4.6. Follow up Procedures (if applicable)

Outcome measures (as highlighted in the above diagram) will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life (QoL) questionnaire, the EORTC QLQ-30 (9).

- commencement of Prehab (T0).
- every two weeks of Prehab
- On Prehab completion (prior to surgery) (T1).
- following surgery at the time of discharge from hospital (T2).
- one-month post-surgery (T3).
- 3 months post-surgery (T4).
- 12-month post-surgery (T5).

Outcome measures will be assessed via the telephone or face to face in the cardiothoracic physiotherapy department at Morriston Hospital, or the satellite center by the CI or research team.

4.7. Laboratory Assessments (not applicable)

4.8. Radiology Assessments (not applicable)

4.9. End of Study Definition

The parameters that will mark the end of the study will be the recruitment of 100 patients with a 12 month follow up period.

4.10. Procedures for unblinding (if applicable)

Blinding: Research team members independent to the Prehab team will analyse the data and outcome measurements of participants and will be blinded to participant group assignment.

The cardiothoracic physiotherapists, managing the post-operative care of patients will be blinded to which group the participant has been randomised to (the intervention arm or control arm).

If a patient is readmitted to hospital following discharge home, it will not be necessary to unblind physiotherapists with the patients new hospital admission. This is because the intervention arms will be pre-operative and will not influence the safety of patients post-operative or influence their medical management.

4.11. Subject Withdrawal

Participants who withdraw/ are withdrawn from the study, will return to standard care without negative consequences. This will be made clear in initial conversations with the research team and a study withdrawal letter will be attached to the PIS, for participants wishing to withdraw at a later stage.

4.12. Data Collection and Follow up for Withdrawn Subjects

All patients will be included in the final data analysis, by using an intention to treat analysis, thereby limiting attrition bias if patients withdraw/ are withdrawn.

5. Safety Reporting

For non-CTIMP reporting, please refer to the safety (other research) procedural table in Appendix 1. For Medical Device reporting, please contact the R&D Office.

The information in this section applies to HRA's expectations for safety reporting. https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/

5.1. General Definitions

5.1.1. Adverse Event (AE)

An AE is any untoward medical occurrence in a subject which is not necessarily caused by or related to the study. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with study activities. There is a possibility of dizziness, coughing, tiredness and a pneumothorax with the inspiratory muscle trainer device.

5.1.2. Serious Adverse Event (SAE)

An SAE fulfils at least one of the following criteria:

- Is fatal – results in death (NOTE: death is an outcome, not an event)
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is otherwise considered medically significant by the Investigator

A report of a Serious Adverse Events (SAEs) that are: **related** to the study (i.e. they resulted from administration of any of the research procedures) and **unexpected** (i.e. not listed in the protocol as an expected occurrence) should be emailed to the REC using the Non-CTIMP safety report to REC form. These should

be sent within 15 days of the chief investigator becoming aware of the event. The completed template must also be emailed to the sponsor within **24 hours** of identifying the SAE: SBU.RandDSafetyReporting@wales.nhs.uk

6. Investigators Assessment

6.1.1. Seriousness

The Chief/Principal Investigator responsible for the care of the patient, or in his absence an authorised medic within the research team, is responsible for assessing whether the event is serious according to the definitions given in section 6.1.

6.1.2. Causality

The Investigator must assess the causality of all serious adverse events in relation to the trial treatment according to the definition given

6.1.3. Expectedness

The investigator must assess the expectedness of all SAEs according to the definition given. If the SAE is unexpected and related, then it needs immediate reporting.

6.1.4. Severity

The Investigator must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term “serious” which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life

Moderate: Discomfort enough to affect/reduce normal activity

Severe: Complete inability to perform daily activities and lead a normal life

6.2. Notification and reporting Adverse Events or Reactions

If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants’ medical notes (where appropriate) and the CRF.

6.3. Notification and Reporting of Serious Adverse Events

Serious Adverse Event (SAEs)

SAEs that are considered to be 'related' and 'unexpected' are to be reported to the sponsor within 24 hours of learning of the event and to the Main REC within 15 days in line with the required timeframe. For further guidance on this matter, please refer to Appendix 2

6.4. Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the trial subjects from any immediate hazard to their health and safety. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor and Main Research Ethics Committee (via telephone) of this event immediately once identified on:
SBU.RandDSafetyReporting@wales.nhs.uk

6.5. Annual Safety Reporting – not applicable

6.6. Procedures for reporting blinded 'unexpected' and related' SAEs – not applicable

6.7. Overview of the Safety Reporting Process

The information will be displayed within a table in appendix 1.

7. Statistical Considerations

7.1. Primary Endpoint Efficacy Analysis

To test our primary hypothesis the chi-square test will be used to assess whether IMT in combination with Prehab is effective in reducing PPCs following lung resection surgery compared with its control i.e., standard Prehab using a significance level of 0.05. 4x4 matrix.

7.2. Secondary Endpoint Efficacy Analysis

Secondary end points include improvement in dyspnoea score, PS, LOA, Frailty, 6MWD test, MIP and QoL. Differences between groups in categorical variables will be tested with Chi square or Fisher's exact test. For continuous data the student's t test or the Mann–Whitney U test will be used. The Wilcoxon signed rank test will be used to compare MIP and QoL at T0 and T1 and T3.

7.3. Safety Endpoints

Safety analysis will include rate of complications and mortality and are categorical data sets. The chi-square test or Fisher's exact test will be used to assess the safety of IMT in combination with Prehab compared with its control i.e., standard Prehab using a significance level of 0.05.

The study may be ended prematurely, if there is a significant increase in post-surgical mortality or complications in the study group.

Additionally, if any of the patients in the intervention group experience syncope symptoms whilst using the device they will be advised to stop and will be withdrawn from the study.

7.4. Sample Size

Please see section 2.4.1. Sample size, justification and calculations

7.5. Statistical Analysis

Our aim is to evaluate the impact of thoracic Prehab with IMT compared to standard Prehab in reducing post operative pulmonary complications following surgical resection in lung cancer patients in a RCT. Statistical analysis will be performed using SPSS statistical software, version 20.0 (IBM Corporation, Armonk, NY, USA). Two-sided significance tests will be used (a\0.05). Data will be presented as mean and standard deviation (SD), or median and interquartile range (IQR) for variables with a skewed distribution. Differences between groups in categorical variables will be tested with Chi square or Fisher's exact test.

For continuous data the student's t test or the Mann–Whitney U test will be used. The Wilcoxon signed rank test will be used to compare MIP and QoL at T0 and T1 and T2.

Relative risk will be calculated for post operative pulmonary complications (PPCs) graded 1-V using the Clavin Dindo classification and impact of IMT on the study group compared to the control group. Assuming a 36.7incidence of PPC after surgery in the control arm and using a significance level of 0.05 and a power of 80%, 50 patients are required in each arm."

8. Data Management

8.1. Data collection

Outcome measures will be collected by the principal investigator and research team onto paper initially, forming part of the physiotherapy notes. These physiotherapy notes will be kept in a locked cabinet within a secure room, which only the PI and research team will have access to.

8.2. Data Systems

Outcome measures collected on paper, will be inputted into a password secure excel database, on a security- protected computer.

8.3. Data integrity

The Good Clinical Research Practice (GCP) guidelines will be followed with regards to maintaining data accuracy and consistency, from data generation, to recording and destruction, including any intervening.

8.4. Data monitoring

Data will be monitored electronically by the whole of the research team and escalated to the CI accordingly.

The data will be reviewed by the CI and PI in a monthly meeting.

8.5. Data archiving and destruction

During the course of research, all records are the responsibility of the CI and will be kept in secure conditions. When the research trial is completed all records will be kept for 5 years, as per requirement of the Research Governance Framework and Health Board Policy that the records are kept for a further 5 years in the Health Board archive facility.

9. Data Handling & Record Keeping

9.1. Confidentiality

The CI has responsibility to ensure that patient anonymity is protected and maintained. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, Research Governance Framework for Health & Social Care 2017 and Research Ethics Committee Approval.

All PIS's will be compliant with the General Data Protection Regulation (2018) (GDPR), ensuring, appropriate transparency of data. All of the study essential documents electronic, and hard copies, will be archived for 5 years, The R&D department will make provisions for archiving and destruction of these documents.

The legal basis for processing and storing/sharing data will be Article 9.2 (j) – pseudo-anonymised (scientific research).

No patient identifiable information will be collected from subjects.

All study participants will be allocated a unique study code and no identifiable data will be captured on the data management system.

As part of the trial, direct, anonymised quotations from participants will be collected. These will be disseminated and published as part of the results of the study. For example, how subjects managed with the device, patient reported experience measures and outcome measures.

9.2. Study Documents

- A signed protocol and any subsequent amendments

- Current Summary of Product Characteristics/ Investigator's Brochure
- Sponsor Self-Monitoring template for the trial team to complete on a regular basis as detailed by the Monitoring section
- Current/Superseded Patient Information Sheets (as applicable)
- Current/Superseded Consent Forms (as applicable)
- Indemnity documentation from sponsor
- Conditions of Sponsorship from sponsor
- Conditional/Final R&D Approval
- Signed site agreement
- Ethics submissions/approvals/correspondence
- CVs of CI and site staff
- Laboratory accreditation letter, certification and normal ranges for all laboratories to be utilised in the study
- Delegation log
- Staff training log
- Site signature log
- Patient identification log
- Screening log
- Enrolment log
- Monitoring visit log
- Protocol training log
- Correspondence relating to the trial
- Communication Plan between the CI/PI and members of the study team
- SAE reporting plan for the study

9.3. Case Report Form/ Data Collection Tool

The research team will be responsible for completing the data collection tool.

9.4. Record Retention and Archiving

During the course of research, all records are the responsibility of the CI and will be kept in secure conditions. When the research trial is completed all records will be kept for 5 years,

as per requirement of the Research Governance Framework and Health Board Policy that the records are kept for a further 5 years in the Health Board archive facility.

9.5. Compliance

The CI will ensure that the trial is conducted in compliance with the principles of the Declaration of Helsinki (1996), and in accordance with all applicable regulatory requirements including but not limited to the Research Governance Framework, Trust and Research Office policies and procedures and any subsequent amendments.

9.6. Clinical Governance Issues

9.6.1 Ethical Considerations

To address issues of geographical location, deprivation, poverty, and for people who are less likely to have access to Prehab due to for example, transport costs, SBUHB Prehab provides satellite clinics closer to patients' homes, or home visits by physiotherapists for the less able. Both male and female patients have equally availed of the service and our Health Board has a robust provision of Equality and Diversity training to all staff working in the Health Board.

The study will be registered with the local NHS Research and Development Department of the Health Board under the guidance of the NHS Research Ethics Centre and commence on receiving ethical approval and conducted to the principles of NIHR Good Clinical Practice in research.

9.7. Quality Control and Quality Assurance

9.7.1. Summary Monitoring Plan

The Sponsor will have the overall responsibility for ensuring the trial is monitored and will have oversight of the process.

The CI will ensure that agreements are in place, the monitoring plan is followed and that the PI is compliant with all monitoring requests.

A completed risk assessment will determine the monitoring required for this study.

9.7.2. Audit and Inspection

Auditing: Definition “A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).”

This study may be identified for audit by any method listed below:

1. A project may be identified via the risk assessment process.

2. An individual investigator or department may request an audit.

3. A project may be identified via an allegation of research misconduct or fraud or a suspected breach of regulations.

4. Projects may be selected at random. The Department of Health states that Health Boards should be auditing a minimum of 10% of all research projects.

5. Projects may be randomly selected for audit by an external organisation.

Internal audits will be conducted by the sponsor’s representative

9.8. Non-Compliance

Patients who do not adhere to the proposed intervention will be offered a telephone consultation, to consider behaviours and characteristics, preferences, barriers and facilitators to enable and explore compliance. This could be done with the carer if the patient wishes. If adherence remains an issue patients will be removed from the research and will be asked to return their patient diary for analysis.

A noted systematic lack of both the CI and the study staff adhering to SOPs/protocol/ICH-GCP, which leads to prolonged collection of deviations, breaches or suspected fraud.

These non-compliances may be captured from a variety of different sources including monitoring visits, CRFs, communications and updates. The sponsor will maintain a log of the non-compliances to ascertain if there are any trends developing which to be escalated. The sponsor will assess the non-compliances and action a timeframe in which they need to be dealt with. Each action will be given a different timeframe dependent on the severity. If the actions are not dealt with accordingly, the research and development Office will agree an appropriate action, including an on-site audit.

10. Trial Committees

A trial management group (TMG) will provide overall supervision for this study and to take steps to reduce deviations from the protocol to a minimum, periodic review of the trials progress, to review safety data and to help resolve any differences within the research team or between the team and trial sponsor. The TMG operates on behalf of the Trial Sponsor and is to ensure that the trial is conducted according to the UK Research Governance Frameworks for Health and Social Care, the principles of Good Clinical Practice (GCP) and all relevant regulation and local policies. The TMG will also ensure the trial runs to time and budget as much as feasible.

The TMG will consist of the chief investigator, principle investigator, study staff and representatives from the sponsor.

The frequency of the TMG will be meet monthly and then quarterly and can be subject to change as the study progresses. An agenda will be sent before each meeting. Minutes of each meeting will be taken, and circulated to the TMG members for accuracy.

11. Intellectual Property

The research question is based upon previous published work and a gap in the literature, identifying a new hypothesis. Appropriate credit to previous published work is provided in the reference section.

All manufacturer names and trademark of equipment are listed below to ensure compliance with trademark laws:

POWERbreathe is the inspiratory muscle trainer to be used in this trial

The CI has obtained permission to use the European Organization for Research and Treatment of Cancer (EORTC) QLQ – C30 QOL questionnaire by completing the online Academic User Agreement.

As this trial is not the development of a device, no intellectual property (IP) will be produced.

12. Publication Policy

The future plans are for amalgamating the two thoracic surgical centres (Cardiff and Swansea) and centralising the service to SBUHB. The newly formed South Wales Adult Thoracic Surgical Service, based at Morriston Hospital, will provide thoracic surgical service to all of South Wales and our Prehab service will be responsible for delivering the Prehab program to lung cancer patients across all of South Wales. Hence, the findings will be shared with patients, public and clinicians of other Health Boards who will be referring patients to our centre. The results will also be shared widely with NHS Trusts outside Wales which provide thoracic surgical services to their population.

The results will be shared widely via the SBUHB web sites with presentations at local and national lung cancer meetings and international conferences. Together with dissemination to cancer charities such as Cancer Research and Tenovus and the authors plan to publish in an appropriate peer review medical journal. The PI will present the findings to her physiotherapy peers within the United Kingdom Thoracic Physio Network. Additionally, a poster presentation will be submitted for the annual meeting of the Society of Cardiothoracic Surgery (SCTC) and the Nursing and Allied Health Professional Sub Committee within this society.

Results will be shared with participants via email or post. Additionally, the research team will explore dissemination via ‘public science’ festivals.

13. Wellbeing of Future Generations Act

This research protocol aligns with the Wellbeing of Future Generations Act, as the introduction of an inspiratory muscle training device within the thoracic Prehab programme at SBUHB, offers the opportunity to make a positive change to current and future lung cancer patients requiring lung resection.

14. References

1. Cancer Research. Lung cancer incidence by age. https://www.cancerresearchuk.org/healthprofessional/cancerstatistics/statistics-by-cancer-type/lung-cancer/incidence#heading-One.

2. Lim E, Baldwin D, Beckles M, Duffy J, et al. Guidelines on the radical management of patients with lung cancer. Thorax. 2010;Suppl 3:1–27.

3. Brunelli A, Kim AW, Berger KI, et al. Physiologic evaluation of the patient with lung cancer being considered for resectional surgery: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e166S–90S.

4. Miskovic A, Lumb A. Postoperative pulmonary complications. British Journal of Anaesthesia. 2017; 118:317-34.

5. Mainini C, Rebelo P, Bardelli R, et al. Perioperative physical exercise interventions for patients undergoing lung cancer surgery: what is the evidence? SAGE Open Medicine. 2016; 4:1-19.

6. Skivington K, Matthews L, Simpson SA, et al. A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021:30;374.

7. Dobkin BH. Progressive Staging of Pilot Studies to Improve Phase III Trials for Motor Interventions. Neurorehabil Neural Repair. 2009 Mar-Apr;23(3):197-206.

8. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004; 240(2):205-213.

9. European Organization for Research and Treatment of Cancer. Available at: https://qol.eortc.org/questionnaires/core/eortc-qlq-c30/

10. The Welsh NHS Confederation (2015). Available at hhtps:www.nhsconfed.org/publications/overview-wellbeing-future-generations-act-2015

11. The Welsh Government Parliamentary Review of Health and Social Care in Wales (2018). Available at hhtps: www.gov.wales/sites/default/files/publications/2018-01/Review-health-social-care-report-final.pdf

12. A Healthier Wales (2018). Available at hhtps: www.gov.wales/healthier-wales-long-term-plan-health-and-social-care

13. Samet JM. Health benefits of smoking cessation. Clin Chest Med. 1991;12(4):669-679.

14. Chesterfield-Thomas Gemma, Goldsmith Ira. Impact of preoperative pulmonary rehabilitation on the thoracoscore of patients undergoing lung resection. Interact

Cardiovasc Thorac Surg 1 November 2016;23(Issue 5):729–32.
15. Goldsmith I, Chesterfield-Thomas G, Toghill H. Pre-treatment optimization with pulmonary rehabilitation in lung cancer: making the inoperable patients operable. E Clinical Medicine. 2021; 31:100663. doi.org/10.1016/j.eclinm.2020.100663.
16. NHS provider results: NLCA State of the Nation Report 2023. Royal college of surgeons of England 2022. https://www.lungcanceraudit.org.uk/reports/nhs-provider-results-nlca-state-of-the-nation-report-2023
17. Figueiredo R, Azambuja A, Cureau F, et al. 'Inspiratory Muscle Training in COPD', Respiratory Care. 2022; 65(8):1189-1201.
18. de Oliveria Vacchi C, Martha B, Macagnan F. Effect of inspiratory muscle training associated or not to physical rehabilitation in preoperative anatomic pulmonary resection: a systemic review and meta-analysis. Supportive Care in Cancer. 2022;30.
19. Mans CM, Reeve JC, Elkins MR. Postoperative outcomes following preoperative inspiratory muscle training in patients undergoing cardiothoracic or upper abdominal surgery: a systematic review and meta-analysis. Clin Rehabil. 2015;29(5):426-38.
20. Katsura M, Kuriyama A, Takeshima T, et al. Preoperative inspiratory muscle training for postoperative pulmonary complications in adults undergoing cardiac and major abdominal surgery. Cochrane Database Syst Rev. 2015 Oct 5;2015(10)
21. Pan XJ, Ou DB, Lin X, Ye MF. Management of Pleural Space After Lung Resection by Cryoneuroablation of Phrenic Nerve: A
Randomized Study. Surg Innov. 2017 Jun;24(3):240-244.
22. Morano MT, Araújo AS, Nascimento FB, et al. Preoperative pulmonary rehabilitation versus chest physical therapy in patients undergoing lung cancer resection: a pilot randomized controlled trial. Arch Phys Med Rehabil. 2013 Jan;94(1):53-8.
23. Matheus GB, Dragosavac D, Trevisan P, et al. Inspiratory muscle training improves tidal volume and vital capacity after CABG surgery. Rev Bras Cir Cardiovasc. 2012 Jul-Sep;27(3):362-9.
24. Satoto HH, Paramitha A, Barata SH, et al. Effects of Preoperative Inspiratory Muscle Training on Right Ventricular Free Wall Longitudinal Strain and ICU Length of Stay in Patients Undergoing Heart Valve Replacement Surgery. Indonesian J Cardiol 2020:41:suppl_A.
25. van Adrichem EJ, Meulenbroek RL, Plukker JT, et al. Comparison of two preoperative inspiratory muscle training programs to prevent pulmonary complications in patients undergoing esophagectomy: a randomized controlled pilot study. Ann Surg Oncol. 2014 Jul;21(7):2353-60.

26. Mark Elkins, Ruth Dentice, Inspiratory muscle training facilitates weaning from mechanical ventilation among patients in the intensive care unit: a systematic review, Journal of Physiotherapy, Volume 61, Issue 3, 2015, Pages 125-134.
27. Bilyy, A., El-Nakhal, T., Kadlec, J., Bartoski, W., Tornout, F., Kouritas, V. 2020. 'Preoperative training education with incentive spirometry may reduce postoperative pulmonary complications', Asian Cardiovascular & Thoracic Annals, 28(9), pp. 592-597.
28. Sweity, E.M., Alkaissi, A.A., Othman, W. et al. Preoperative incentive spirometry for preventing postoperative pulmonary complications in patients undergoing coronary artery bypass graft surgery: a prospective, randomized controlled trial. J Cardiothorac Surg. 2021;16: 241.
29. Guowei Che, et al. Seven-day intensive preoperative rehabilitation for elderly patients with lung cancer: A Randomized controlled trial. Interactive CardioVascular and Thoracic Surgery. 2017;25(1).
30. Komici K, Bencivenga L, Neal N, et al. Frailty in Patients with Lung Cancer a Systematic Review and Meta-Analysis. Chest. 2022;2:22. doi.org/10.1016/j
31. Spruit, M. A. et al. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. Am J Respir Crit Care Med. 2013;188, e13–e64.
32. Falcoz P.E., Conti M., Brouchet L., et. al.: The Thoracic Surgery Scoring System (Thoracoscore): risk model for in-hospital
death in 15,183 patients requiring thoracic surgery. J Thorac Cardiovasc Surg 2007; 133: pp. 325-332.
33. Detterbeck FC, Boffa DJ, Kim AW, Tanoue LT. The eighth edition lung cancer stage classification. Chest 2017;151(1):193–203. doi: 10.1016/j.chest.2016.10.010.
34. Sealed envelope LTD, 2019. Available: https://www. sealedenvelope. com/ simplerandomiser/v1/).
35. Hulzebos EH, Helders PJ, Favié NJ, de Bie RA, Brutel de la Rivière A, van Meeteren NL. Minder longcomplicaties door ademspiertraining bij patiënten die een coronaire bypassoperatie moeten ondergaan: een gerandomiseerde trial [Fewer lung complications following inspiratory muscle training in patients undergoing coronary bypass surgery: a randomized trial]. Ned Tijdschr Geneeskd. 2007 Nov 10;151(45):2505-11.

15. Appendices

The following is a list of attachments, those with an asterisk* must be submitted to the Research Ethics Committee with the protocol:

Appendix 1 – Information with regards to safety reporting in Non-CTIMP research. Page 45 to 46

Appendix 2 – Source Identification List. Page 47

Appendix 1 – Information with regards to Safety Reporting in Non-CTIMP Research

https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/safety-reporting/safety-and-progress-reports-other-research-procedural-table/

Annual Progress Report link

https://www.hra.nhs.uk/documents/2996/Annual_Progress_Report_Form_other_research_July_2022_v_4.7_final.odtsm.docx

End of study report link

Submit your Final Report - Health Research Authority (hra.nhs.uk)

What and type	Who	When	How	To Whom
SAE	Chief Investigator	-Report to Sponsor within 24 hours of becoming aware of the event Report to the MREC within 15 days of becoming aware of the event	SAE report form for non- CTIMPs, available from the HRA website.	Sponsor and REC which issued the favourable ethical opinion.
Urgent Safety Measures	Chief Investigator or Sponsor. Or exceptionally by the local Principal Investigator (PI).	Immediately (by telephone) Within 3 days (in writing)	By telephone Noting in writing setting out the reasons for the urgent safety measures and the plan for further action.	To Sponsor and REC which issues the favourable ethical opinion. Approvals Officer/REC Manager will acknowledge within 30 days.
Declaration of the conclusion or early termination of the research	Chief Investigator or Sponsor	Within 90 days (conclusion). Within 15 days (early termination).	End of study declaration (EOSD) form, available from the HRA website.	The REC which issued the favourable ethical opinion.

		The end of the trial should be defined in the protocol.	Please also email the EOSD to Sponsor	
Final Report **Note: This is only applicable for project-based research (i.e., not research tissue banks or research databases) that have received a favourable ethical opinion from a REC**	Chief Investigator	Within one year of conclusion of the Research	Final Report, submitted via the HRA website or via IRAS, depending on the type of study.	Submitted centrally to the research ethics service.

All reports will be acknowledged within 30 days. If any issues are raised, the REC may write to the Chief Investigator or sponsor for further information or clarification

Appendix 2

Source Data Identification List

No patient identifiable information will be collected from subjects.

All study participants will be allocated a unique study code and no identifiable data will be captured on the data management system.

Communication Plan

The Chief Investigator: will oversee the running of the trial, data management and analysis, publishing, presenting and disseminating the results.

The Principal Investigator: will oversee and ensure trial is conducted to agreed protocol, legal requirements and participant welfare. In addition, communicating with the research team, reporting adverse events, and publishing, presenting and disseminating results.