Effectiveness and cost-effectiveness of INSPIRatory muscIE training (IMT) for reducing postoperative pulmonary complications (PPC): a sham-controlled randomised controlled trial (RCT) (INSPIRE)

Statistical Analysis Plan

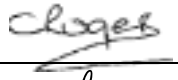
Role	Name	Signature	Date
Study Statistician	Russell Thirard		14/08/2024
Authorising Statistician	Chris Rogers		14/08/2024
Chief Investigator	Maria Pufulete		15/08/2024
Clinical Lead	Denny Levett		

Table of contents

1. Introduction

1.1 Summary of document

1.1.1 Scope

The statistical analysis plan (SAP) for the Inspire study has been written in accordance with Bristol Trials Centre (BTC) standard operating procedures, the CONSORT statement, and International Conference on Harmonisation (ICH) Statistical Principles for Clinical Trials E9, by Russell Thirard, statistician at the BTC, under the supervision of Professor Chris Rogers, senior statistician, and covers all statistical analyses to be performed. The SAP only covers statistical analyses excluding health economics and qualitative analyses.

1.1.2 Planned analyses and dissemination

The end of study statistical report will be disseminated to the TMG when all pre-specified final analyses have been performed. An independent data monitoring and safety committee (DMSC) will review the safety and ethics during the study. The DMSC, in light of the interim reports and of any advice or evidence they wish to request, will report to the Trial Steering Committee (TSC) if there are any concerns regarding the safety of the intervention or ethics of the study.

Recruitment to study was slower than planned and in May 2022, the funder confirmed the closure of the study. The study contract was extended to cover recruitment up to the end of Phase 1 (pilot) and follow-up of recruited participants up to 6 months. This SAP reflects changes made to the study and reduced sample size.

Sections 1, 2 and 3 reflects the original study design (Phase 1 and Phase 2) as described in the protocol.

1.2 Background of study

1.2.1 Study rationale

1.2.2 Aims and objectives

The INSPIRE study will compare the effectiveness, cost-effectiveness and safety of high resistance inspiratory muscle training (IMT) (minimum 2 weeks before surgery) versus low resistance IMT intervention (fixed low resistance IMT) or usual care in reducing postoperative pulmonary complications (PPCs) in participants at high risk of PPCs undergoing elective major surgery.

Specific objectives are to estimate:

1. The optimal mode of delivery for the IMT intervention;
2. The difference between groups in the incidence of PPCs after surgery;
3. The difference between groups with respect to a range of secondary outcomes including: individual components of the primary outcome; postoperative ventilation; length of intensive care unit (ICU) stay; length of hospital stay; antibiotic prescription; bronchodilator prescription; health-related quality of life (HRQoL); maximal inspiratory pressure (MIP), spirometry (forced expiratory volume, FEV_1 and forced vital capacity, FVC) and mortality;

2. Study methods

2.1 Design

The INSPIRE study is a pragmatic parallel, 3 group RCT (with an internal pilot) with high resistance IMT, low resistance IMT and usual care interventions. We will compare usual care, with IMT (highest tolerable load) with fixed low resistance IMT, which has been used effectively in previous successful trials of IMT in other clinical contexts [26, 27] in 2500 patients. In current UK clinical practice, usual care does not usually include IMT, although may include other prehabilitation interventions such as exercise or dietary modifications to improve outcomes after surgery. In the internal pilot (Phase 1) we will also conduct a study within a trial (SWAT) on approximately 321 patients (this is the number of patients we expect to recruit based on projected recruitment rate over eight months).

2.1.1 Internal pilot (Phase 1)

INSPIRE will have an internal pilot (Phase 1) to:

i. describe recruitment rates;
ii. describe participants' adherence to the IMT protocol (i.e. following the instructions to carry out IMT twice per day at the correct intensity);
iii. determine whether an additional 'virtual' follow up meeting conducted via telephone or video call (within one week of starting the intervention, ideally day 3 to 5) improves adherence to the IMT protocol and the effectiveness of the training as determined by the progression in training load;
iv. determine whether adjusting the training load automatically using the IMT device improves adherence to the IMT protocol and the effectiveness of the training as determined by the progression in training load;
v. determine whether there is any contamination between intervention and control groups.

Phase 1 will define the optimal mode of delivery of the IMT intervention, which will be used in the main trial (Phase 2). Phase 1 will take place in a minimum of four UK hospitals.

2.1.2 Study within a trial (SWAT)

We will include a study within a trial (SWAT) in participants randomised to high-resistance IMT in Phase 1 of the trial. The SWAT will be a factorial trial to evaluate the benefit of two modes of delivery of the IMT intervention: an additional 'virtual' follow up meeting conducted via telephone or video call with the research nurse or physiotherapist within one week of starting IMT to check that participants are following the IMT protocol and training at the correct intensity; and the use of the automatic load adjusting function on the IMT device to increase the training load automatically, so that patients do not have to do this manually. The two modes of delivery will be compared with respect to the primary outcome. Participants will be randomised to one of four groups as described in Table 1 and below:

Table 1: Factorial 2x2 design table

	Automatic load adjustment to increase training load	Manual load adjustment to increase training load
One additional 'virtual' follow up meeting	AV	MV
No additional 'virtual' follow up meeting	AN	MN

AV Automatic load adjustment and one additional 'virtual' follow up meeting;
MV Manual load adjustment and one additional 'virtual' follow up meeting;
AN Automatic load adjustment and no additional 'virtual' follow up meeting;
MN Manual load adjustment and no additional 'virtual' follow up meeting.

Automatic load adjustment (using the automatic function on the IMT device to increase training load) vs. manual increase of training load

i) Automatic load adjusting function to increase training load

Participants will make use of the automatic load adjusting function on the IMT device to increase the training load in response to training adaptation, i.e. MIP is estimated at the beginning of each training session and the training load is adjusted automatically by the device, without the user having to increase the training load manually. Participants will record training sessions in the paper diary and rate the intensity of each training session using the RPE rating scale for ratings of perceived exertion (RPE rating scale from 0-10) which can be found in the appendix (Figure 2).

ii) Manual load adjustment to increase training load

Participants will increase the training load manually based on their perceived exertion measured using the RPE rating scale. An RPE rating at the end of a training session of 5 or less will signify that the load should be increased by 5% (participants will be supplied with a table of pre-calculated training loads as shown in Figure 3). Participants will record training sessions and RPE ratings in the paper diary.

Additional 'virtual' follow up meeting vs no additional 'virtual' follow up meeting

i) One additional 'virtual' follow up meeting

Participants in the high resistance IMT group will receive an additional follow up meeting conducted via telephone or video call within one week of the initial IMT training session (ideally day 3 to 5). The research nurse or physiotherapist will assess adherence and progression of the training load and will provide further training or support where it is required (section 5.6.3). Participants will have been provided with and may have watched a step-by-step digital recording (video) on how to use the device at the initial IMT training session and will have also been provided with written information, a paper training diary for recording training sessions, and telephone support in the form of a helpline number that participants can call (if they have any queries or require assistance). Within the training diary they will be asked to rate their perceived exertion using the RPE rating scale after each training session.

ii) No additional 'virtual' follow up meeting

Participants will attend the initial IMT training session with a research nurse or physiotherapist but participants will not receive an additional virtual follow up meeting.

SWAT primary outcome

The primary outcome of the SWAT will be the progression in training load from baseline. The secondary outcomes will be:

- Change in work (recorded on the IMT device) from baseline;
- Change in MIP from baseline;
- Change in spirometry markers (FEV_1 and FVC) from baseline;

- Proportion of participants following at least 80% of the planned training sessions;
- Proportion of participants training at the prescribed intensity score of (RPE rating) ≥5.

We will consider removing the additional 'virtual' follow up meeting in Phase 2 if the increase in training load from baseline in the no additional 'virtual' follow up meeting group is similar to that in the additional 'virtual' follow up meeting group. We will consider automatic load adjustment in Phase 2 if the increase in training load from baseline in the automatic group is similar to that of the manual group. We will take into account any important interactions between the two interventions (loading method with or without an extra 'virtual' follow up meeting) when making the final decision regarding the delivery of the intervention in Phase 2.

SWAT sample size

It is planned to recruit 160 participants to the high intensity IMT during Phase 1; 40 per each of the four treatment combinations. The SWAT will provide 95% confidence intervals of width +/- 0.31 standard deviations in progression of training load for the main effects of visit and method load adjustment and 95% confidence intervals of width +/- 0.45 standard deviations for comparisons between load method when an extra visit is included and separately between load method when an extra visit is not included.

2.1.3 Main study (Phase 2)

Progression criteria from Phase 1 to Phase 2:

- all centres participating in the pilot are recruiting (in one or more specialties);
- at least 40% of eligible patients are consenting to randomisation;
- each centre recruiting >8 patients/month (from any specialty);
- interventions are delivered according to the protocol in all centres;
- the allocated intervention is initiated in >=90% of randomised participants;
- >=70% of patients randomised to high resistance IMT or low IMT adhere to allocated interventions (adherence will be recorded electronically by the IMT device); we will define a patient as adherent with the intervention if they use the IMT device at least five days a week (for a minimum of 30 breaths per day).

If progression criteria are met, recruitment will continue at the Phase 1 hospitals and we will begin recruitment at a minimum of an additional two hospitals (depending on how recruitment is going in Phase 1). Delivery mode of the intervention will be based on the findings in Phase 1 and any amendments to the study will be submitted for approval by the regulatory authorities.

2.1.4 Setting

Phase 1 of the study will take place in a minimum of four NHS secondary care hospitals, in one or more surgical specialties (section 5.5). A Principal Investigator (PI), (consultant surgeon from one of the surgical specialties, consultant in perioperative medicine, or physiotherapist with expertise in IMT) will be appointed from each hospital. A small number of research nurses or physiotherapists from each hospital will be trained and deliver the intervention to all participants recruited. In Phase 2 recruitment will be extended to a further two or more centres.

2.2 Randomisation

Randomisation will be carried out after eligibility has been confirmed and consent given, and baseline measurements have been made. Randomisation will be performed by an authorised member of the local research team using a secure internet-based randomisation system ensuring allocation concealment. Participants will be randomised in a 2:1:1 ratio to: i) high resistance IMT ii)

low resistance IMT or iii) usual care (no IMT and written instructions on deep breathing exercises). The random allocation will be stratified by centre and specialty, so that each speciality at each centre will have approximately equal numbers of participants allocated to the high resistance IMT group and low resistance IMT group/usual care. As the study is not evaluating the surgery per-se, surgical experience is not a criterion for participation (all participants will be under the care of a consultant surgeon). In the context of this study, clustering by surgeon is not relevant to the sample size and can be ignored (on the basis that the intraclass correlation is negligible; personal communication with Prof D Altman for a previous study).

2.3 Framework

The main aim of the study is to compare the number of lung complications between the three groups in the first 30 days after surgery. We will record whether a lung complication develops in hospital whilst patients are recovering from surgery or causes hospital admissions after patients are discharged from hospital following their operation. We will also compare the time patients spend in hospital, their quality of life after their operation and survival.

The study will be conducted in two phases, Phase 1 (pilot) and Phase 2 (main study). In Phase 1, we will determine whether we can recruit participants in the study and whether they perform their exercises as instructed. We also will evaluate (in participants receiving high intensity IMT only) whether either of two interventions: (A) an additional 'virtual' follow up meeting conducted via telephone or video call; (B) using the algorithm built into the POWERbreathe K-series to estimate maximal inspiratory pressure (MIP) and increase device load automatically; improves adherence to IMT and results in more participants performing the IMT exercises correctly. If Phase 1 shows that we can recruit enough participants according to our progression criteria (section 5.2.6) and that they can perform their exercises as instructed in the protocol, we will move to Phase 2.

2.4 *Sample size*

2.4.1 Study sample size

We will recruit 2,500 participants (1250 high resistance IMT, 625 low resistance IMT and 625 usual care), providing 90% power to detect a 5% difference in the primary outcome (of any PPC versus no PPC; 20% vs 15%, risk ratio 0.75) between high resistance IMT versus low resistance IMT and usual care combined. We do not anticipate a difference between the low resistance IMT and usual care groups and will be able to quantify a zero difference with a 95% CI of width +/- 4.5%. In addition, the study will have 75% (90%) power to detect a difference of 15% (14%) versus 20% between the high intensity and low intensity groups, or between the high intensity and usual care groups.

2.4.2 SWAT Sample size

It is planned to recruit 160 participants to the high intensity IMT during Phase 1; 40 per each of the four treatment combinations. The SWAT will provide 95% confidence intervals of width +/- 0.31 standard deviations in progression of training load for the main effects of visit and method load adjustment and 95% confidence intervals of width +/- 0.45 standard deviations for comparisons between load method when an extra visit is included and separately between load method when an extra visit is not included.

2.5 Blinding

The study includes a low resistance IMT intervention group, set to a resistance level that is considered ineffective in influencing MIP [27]. This group has been included so that participants,

their clinical care team (i.e. surgeon, anaesthetist and post-operative care team) and all members of the research team with the exception of those administering the IMT interventions can be blind to participants' allocation to high/low resistance IMT. The research nurses or physiotherapists administering the low and high resistance IMT interventions will obtain the allocation from the internet system and will not be blind to allocation.

Some participants in the low resistance IMT group may discern that they are not doing the 'real' IMT intervention, since their training load will be constant (i.e. will not increase) throughout the intervention period. However, the risk of unblinding is reasonably low since surgical patients are unlikely to be familiar with the concept of IMT and so will not know what real IMT feels like. Furthermore, there have been no side effects reported from performing IMT in various patient populations, so patients are unlikely to be unblinded because of any side effects attributed to IMT. Care will be taken to prevent the opportunity for conversation between participants allocated to low and high resistance IMT to avoid the risk of contamination.

The PIL and the process of informed consent will describe the study in terms of testing different types of 'breathing exercises' (with and without a device) and explain the uncertainty around the potential beneficial effects of these exercises. Therefore, the participant should not have a strong expectation that one or other types of breathing exercises should lead to fewer complications after surgery. Participants will be made aware before entering the study that the study involves breathing exercises performed with a device (IMT) or without a device but they will not be told specifically that there are high and low resistance IMT training groups. The unique code provided by the randomisation system will provide the intervention as specified according to the pre-determined randomisation list drawn up by the study statistician prior to recruitment. The allocations will only be known by individuals administering the interventions and the study statistician responsible for generating the allocation scheme and for producing unblinded analyses and will not be disclosed to any other member of the research team.

3. Populations

3.1 Study populations

We will recruit participants undergoing major elective cardiac surgery (on the heart and great vessels carried out via a midline sternotomy); thoracic surgery (open or minimal access surgery on the lungs and surrounding tissues); or abdominal surgery (open or minimal access surgery within the abdominal cavity/intraperitoneally); (oesophageal, gastric, hepatobiliary, colorectal, gynaecological, urological, or open aortic aneurysm repair). These patient populations have been chosen because they have a high incidence of PPCs [1, 2]. We will include both open and laparoscopic (including robotic) surgery for generalisability, as a significant proportion of abdominal surgery is conducted laparoscopically.

We will include only participants at high risk of PPCs (20% incidence) identified using the ARISCAT score as shown in Figure 1 (≥26; based on age, arterial oxyhaemoglobin saturation by pulse oximetry, respiratory infection in previous month, preoperative anaemia (Hb ≤10 g/dl), site of surgical incision, > 2hr predicted duration of surgery [1]). These components are easily assessed preoperatively and will be available for most participants at the time of recruitment. The ARISCAT score has been validated in our participant population [2].

Figure 1: The seven ARISCAT predictors of risk of PPCs

	β Regression Coefficients	Score
Age (yr)		
≤50	0	0
51–80	0.331	3
>80	1.619	16
Preoperative Spo_2		
≥96%	0	0
91–95%	0.802	8
≤90%	2.375	24
Respiratory infection in the last month		
No	0	0
Yes	1.698	17
Preoperative anemia (Hb ≤10 g/dl)		
No	0	0
Yes	1.105	11
Surgical incision		
Peripheral	0	0
Upper abdominal	1.480	15
Intrathoracic	2.431	24
Duration of surgery (h)		
<2	0	0
2–3	1.593	16
>3	2.268	23
Emergency procedure		
No	0	0
Yes	0.768	8

*Three levels of risk were indicated by the following cutoffs: <26 points, low risk; 26–44 points, moderate risk; and ≥45 points, high risk.

ARISCAT = Assess Respiratory Risk in Surgical Patients in Catalonia; Hb = hemoglobin; SpO_2 = arterial oxyhemoglobin saturation by pulse oximetry.

3.1.1 Inclusion criteria

Participants may enter the study if ALL of the following apply:

1. *Age ≥18*
2. *Elective major cardiac, thoracic and abdominal surgery (oesophageal, gastric, hepatobiliary, colorectal, gynaecological, urological, or open aortic aneurysm repair) under general anaesthesia, including both open and laparoscopic surgery*
3. *ARISCAT score ≥26 [1]*
4. *At least 14 days until planned operation date*
5. *Able to give informed consent*

NB: Participants who fulfil each of the criteria listed above and are undertaking a prehabilitation programme as part of usual care at their hospital **can** be included in the study.

3.1.2 Exclusion criteria

Participants may not enter the study if ANY of the following apply:

1. *Emergency surgery*
2. *Unable to participate in the intervention (e.g. have cognitive impairment)*
3. *Lack capacity to consent*
4. *Recent cardiac, thoracic or open abdominal surgery (in previous 2 months)*
5. *Prisoners*
6. *Patients with a history of spontaneous pneumothorax (if a patient has had a traumatic pneumothorax and are fully recovered, then they can be included)*
7. *Eardrum perforation within 6 weeks*
8. Phrenic nerve palsy

3.2 Data sources

Outcome data will be collected using a purpose-designed database. Where the trial database is the site of original recording this will be considered source data. Data will be captured at several timepoints including screening, from admission for surgery to discharge and followed-up for up to 6 months.

Where the database isn't the original recording the source data will include, but is not limited to medical history, medication records, vital signs, physical examination records, and questionnaire responses.

Table 2 Data collection schedule

Data item	**Baseline** ***(Pre-randomisation)***	**Initial training visit*** ***High/low resistance IMT/usual care groups***	***Additional virtual follow up*** ***<u>High resistance IMT group: Phase 1 only</u>***	**Pre-surgery**	**In hospital**	**Discharge**	**3 months post-surgery**	**6 months post-surgery**
Socio-demographic details	✓							
Co-morbidities	✓							
Routine CPET parameters#				✓				

Maximal inspiratory pressure (MIP)		✓		✓				
Spirometry		✓		✓				
Check on adherence and progression of the IMT training load[§]			✓	✓				
Routine clinical measures	✓	✓		✓	✓	✓		
PPCs					✓	✓	✓	✓
Resource use schedule					✓	✓	✓	✓
SF-12	✓			✓			✓	✓
EQ-5D-5L	✓			✓			✓	✓
MUST & PONS assessments				✓				
DASI questionnaire	✓							✓
HADS, CDRQ & self-efficacy questionnaires	✓							✓
Surgical regret questionnaire								✓
Adverse events			✓	✓	✓	✓		
Serious adverse events			✓	✓			✓	✓

[*] High resistance IMT/low resistance IMT training can be at POA appointment if more than 2 weeks before surgery. An additional visit will need to be booked if POA appointment is less than 2 weeks before surgery.

3.3 Analysis populations

3.3.1 Intention-to-treat population

Analyses and summaries will be performed on an intention-to-treat basis. Analyses will use data from all participants randomised. The ITT population will consist of all randomised participants, included according to their randomised allocation, regardless of whether they are ineligible, prematurely discontinue treatment or are otherwise protocol deviators.

3.3.2 Per-protocol population

An analysis of the primary outcome on the per-protocol population will be considered if there are a considerable number of major protocol deviators (>5% of the ITT analysis population).

The following types of protocol deviation will be considered:

- Participant did not meet the study eligibility criteria but was treated in the study
- Participant did not receive/adhere to allocated intervention

Note, it may be possible for participants to be classified as a protocol deviation for more than one reason.

The frequency of each type of deviation will be tabulated by treatment allocation (see Table A8).

3.3.3 Safety population

The safety population will consist of all randomised participants. Participants will be grouped according to treatment received.

3.4 Withdrawals

Each participant has the right to withdraw at any time for any reason and is not obliged to give their reasons for doing so. Data collected prior to withdrawal will be retained and reported.

A clinician may withdraw a participant at any time if they feel it is in the participant's best interests (e.g., a clinical reason for not performing the surgical procedure is discovered, not possible due to their health).

Reasons for all discontinuations and withdrawals will be captured in the trial database and reported.

The DMSC may recommend cessation of treatment for participants.

4. Statistical analyses and report content

4.1 General considerations

The statistical analysis is the responsibility of the BTC study statisticians.

Where interventions are being compared formally using statistical modelling, the usual care and low-resistance IMT groups combined will act as the reference category (see section for 4.4.1 for discussion of initial analysis).

All statistical tests will be superiority comparisons; they will be 2-sided and will be performed using a 5% significance level, with the exception of tests for interactions that will be performed using a 10% significance level.

No formal adjustment will be made for multiple testing, but consideration will be taken in interpretation of results to reflect the number of statistical tests performed and the consistency, magnitude and direction of treatment estimates for different outcomes.

4.2 General calculations

Unless otherwise stated, all percentages will be calculated using the total number of participants from the relevant population as the denominator. For categorical and binary data, all percentages will be rounded to 2 decimal place(s), and for continuous measures, these will be summarised to one more decimal place than the data is collected, etc. P-values >0.001 will be summarised to 2 significant figures, and those <0.001 will be reported as <0.001.

4.3 Outcomes

4.3.1 Primary outcome

The primary outcome will be the incidence of any PPC (a yes/no binary outcome) occurring in-hospital (before discharge) or hospital readmission for a PPC within 30 days from surgery in each of the three care groups.

New variable	Rules
Incidence of any PPC	**YES:** (Any postoperative pulmonary complications in-hospital) OR (Any Hospital readmission for postoperative pulmonary

	complications within 30 days following surgery) **NO:** (NO postoperative pulmonary complications in-hospital) AND (NO Hospital readmission for postoperative pulmonary complications within 30 days following surgery) **MISSING:** otherwise

4.3.2 Secondary outcome

New variable	Rules
Respiratory infection	**YES:** If participant treated with antibiotics for a respiratory infection, plus at least one of the following criteria: - New or changed sputum; - New or changed lung opacities on a clinically indicated chest radiograph; - Temperature >38.3°C; - Leukocyte count >12,000/mm3 in hospital or during a hospital admission within 30 days of surgery **NO:** If participant did not have a respiratory infection (defined above) in hospital or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Respiratory failure	**YES:** If (postoperative PaO2 <60 mmHg (<8kPa) on air OR a ratio of PaO2 to inspired oxygen fraction <300) OR (arterial oxyhaemoglobin saturation <90% AND participant required oxygen therapy) **NO:** If arterial blood glasses taken AND (postoperative PaO2 ≥60 mmHg (≥8kPa) on air AND a ratio of PaO2 to inspired oxygen fraction ≥300) AND (arterial oxyhaemoglobin saturation ≥90% OR participant did not require oxygen therapy) **NO:** arterial blood glasses NOT taken AND (arterial oxyhaemoglobin saturation >=90% OR participant did not require oxygen therapy) **MISSING:** otherwise
Pleural effusion	**YES:** If participant did have a pleural effusion in hospital or during a hospital admission within 30 days of surgery

	NO: If participant did not have a pleural effusion in hospital or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Atelectasis	**YES:** If participant did have atelectasis hospital or during a hospital admission within 30 days of surgery **NO:** If participant did not have atelectasis in hospital or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Pneumothorax	**YES:** If participant did have a pneumothorax failure in hospital or during a hospital admission within 30 days of surgery **NO:** If participant did have a respiratory failure in hospital or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Aspiration pneumonitis	**YES:** If participant did have a respiratory failure in hospital or during a hospital admission within 30 days of surgery **NO:** If participant did have a respiratory failure in hospital or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Invasive ventilation	**YES:** If participant did have a mechanical ventilation in hospital post operatively or during a hospital admission within 30 days of surgery **NO:** If participant did not have a mechanical ventilation in hospital post operatively or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Non-invasive ventilation (including continuous positive airway pressure (CPAP) and/or pressure support (BIPAP))	**YES:** If participant did have non-invasive ventilation (NIV) ventilatory support via a facemask/hood post operatively or during a hospital admission within 30 days of surgery **NO:** If participant did not have non-invasive ventilation (NIV) post operatively or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Optiflow (high flow nasal oxygen therapy)	**YES:** If participant did have high flow nasal oxygen (optiflow) in hospital post operatively or during a hospital admission within 30 days of surgery

	NO: If participant did not have high flow nasal oxygen (optiflow) in hospital post operatively or during a hospital admission within 30 days of surgery **MISSING:** otherwise
Length of ICU stay	= (ICU discharge date – ICU admission date)
Length of hospital stay	= (Hospital discharge date – surgery date)
Antibiotic prescription	**YES:** If participant was prescribed antibiotic for one or more PPC within 6 months following surgery **NO:** If participant was not prescribed antibiotic for one or more PPC within 6 months following surgery **MISSING:** otherwise
Bronchodilator prescription	**YES:** If participant was prescribed bronchodilator within 30 days following surgery **NO:** If participant was not prescribed bronchodilator within 30 days following surgery **MISSING:** otherwise
EQ5D single summary index score	Five digit 'state' score is derived as: 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score. Each state score is then assigned a single summary index score according to reference scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health.
HADS	Each question is assigned 0 to 3 (4 point scale). Each question contributes to either Depression score or for the Anxiety score. The total score is calculated as the sum for the Depression and for the Anxiety.
Connor Davidson Resilience Questionnaire	Scoring of the scale is based on summing the total of all items, each of which is scored from 0-4. For the CD-RISC-10, the full range is therefore from 0 to 40.
Self-efficacy using the Lorig self-efficacy questionnaire	The score for each item is the number circled. The numbers range from 1 to 10. If two consecutive numbers are circled, the lower number (less self-efficacy) is coded. The score for the scale is the mean of the six items. **MISSING:** If more than two items are missing, the scale score is missing.

Physical activity using the Duke Activity Status Index (DASI)	Each item is attributed a score from 1.75 to 8.0. If the answer is YES, the item score contributes to the total score. If NO, a score of 0 is added to the total score. **MISSING**: 5 out of the 12 questions or less are reported, the DASI score would be considered missing or incomplete
Change in maximal inspiratory pressure (MIP)	= MIP on day of surgery – MIP at baseline
Change in Spirometry (forced expiratory volume, FEV_1 and forced vital capacity, FVC) measurements	= Spirometry metric on day of surgery – spirometry metric at baseline
Mortality (in-hospital)	**YES:** Death recorded in hospital **NO:** Participant was discharge from hospital **MISSING:** otherwise
Mortality (to 30 days)	**YES:** Death recorded within 30-days following surgery **NO:** Participant alive at 30-days following surgery **MISSING:** otherwise
Comprehensive Classification Index	Each Clavien-Dindo grade is assigned a weight. For instance, single complications are given weights as below: • Grade I: 8.7 • Grade II: 20.9 • Grade IIIa: 26.2 • Grade IIIb: 33.1 • Grade IVa: 42.1 • Grade IVb: 50.0 • Grade V: 100.0 For multiples complications, the score is derived as the square root of the sum of all [(MRVphys × MRVpat)] and then divided by 2. This will provide a score between 0 and 100. The median (ratings are not normally distributed) reference value from physicians (MRVphys) and patients (MRVpat) for each grade are available at http://links.lww.com/SLA/A405.

SWAT primary outcome

The performance of IMT will be defined by the progression in training load from baseline.

SWAT secondary outcomes

- Change in work (recorded on the IMT device) from baseline;
- Change in MIP from baseline;
- Change in spirometry markers (FEV_1 and FVC) from baseline;
- Proportion of participants following at least 80% of the planned training sessions;
- Proportion of participants training at the prescribed intensity score of (RPE rating) ≥5

New variable	Rules
Change in load	= load on last line of patients diary – load at initial training visit
Change in work	= work in joules on last line of patients diary – work in joules at initial training visit
Change in MIP	= MIP on day of surgery – MIP at baseline
Change in spirometry markers (FEV_1 and FVC) from baseline	= FEV_1 on day of surgery – FEV_1 at baseline = FVC on day of surgery – FVC at baseline
Proportion of participants following at least 80% of the planned training sessions – recorded on patient diary	**YES:** If more than 22 (80% of planned 28) energy measurements are recorded on the patient diary **NO:** If 22 or less (80% of planned 28) energy measurements are recorded on the patient diary **MISSING:** otherwise
Proportion of participants following at least 80% of the planned training sessions – recorded on KHP2 device	**YES:** If more than 22 (80% of planned 28) energy measurements are recorded on the KHP2 device **NO:** If 22 or less (80% of planned 28) energy measurements are recorded on the KHP2 device **MISSING:** otherwise
Proportion of participants training at the prescribed intensity score of RPE rating ≥5	**YES:** If participant reported an RPE of 5 and above on their first, second and last line of patients diary **NO:** If participant reported at least one RPE below 5 on their first, second or last line of patients diary **MISSING:** otherwise
Proportion of participants training at the prescribed intensity score of RPE rating ≥5 – additional visit measurements	**YES:** If participant reported all RPE values of 5 and above during the most recent 10 training sessions at their additional visit

(participants randomised to additional visit only)	**NO:** If participant reported at least one RPE below 5 during the most recent 10 training sessions at their additional visit **MISSING:** otherwise

Adherence to inspiratory muscle training

The success of IMT will be defined by the adherence of participants to the intervention.

New variable	Rules
IMT adherence	**YES:** • >= 1 IMT session initiated on >= 5 days / week during >= 2 weeks after randomisation AND • >= 30 breaths overall completed on each day **NO:** • < 1 IMT session initiated on >= 5 days / week during >= 2 weeks after randomisation OR • >= 1 IMT session initiated on < 5 days / week during >= 2 weeks after randomisation OR • >= 1 IMT session initiated on >= 5 days / week during < 2 weeks after randomisation OR • < 30 breaths overall completed on each day **MISSING:** otherwise

Success of participant blinding using the Bang Blinding Index

The success of participant blinding will be inferred from blinding indices.

New variable	Rules
Blinding indices	Blinding indices will be calculated using the method proposed by Bang et al.

4.4 Analysis of the outcomes

4.4.1 First stage to the analysis

There are insufficient data to support any statistical basis for combining the usual care and low IMT groups as planned, therefore the planned first stage of analysis comparing low resistance IMT and usual care groups will not be performed. Instead, the primary and secondary outcome data will be described by the three groups separately, as well as the combined low resistance IMT/usual care group. The primary analysis of the study will compare the high resistance IMT

group with the combined low IMT/usual care groups as the hypothesis was that the low resistance IMT would not differ to usual case and the sample size per group was set on that basis.

4.4.2 Adjustment in models

For continuous outcomes that are measured before the treatment has started at baseline as well as subsequently, subsequent values will be modelled, and the baseline value will be modelled as a fixed covariate. Models will be adjusted for stratification factors.

4.4.3 Analysis models

General methods of presentation and assessing treatment effects for all outcomes are outlined below according to data type. As the trial was halted early, only the primary outcome of the trial and the primary outcome of the SWAT will be formerly modelled. The secondary outcomes will be tabulated by treatment group but will not be modelled (i.e. the difference between groups will not be quantified).. The secondary outcomes of the SWAT will be tabulated following the 2x2 factorial design groups.

Data type	Outcomes
Binary	• Proportion of participants with any PPC
Continuous	• Load (SWAT outcome)

Each data type will be summarised and compared between the groups according to the following:

- Binary outcomes will be presented as numbers and percentages of participants in each treatment group. Outcomes will be compared between treatment groups using generalised linear models, with treatment comparison estimates presented as adjusted risk ratios (RR) and risk differences (RD) with 95% CIs.
- Continuous outcomes will be summarised as means and SDs (or medians and IQRs if distributions are skewed). Outcomes will be compared using linear mixed effects methodology with treatment groups and study design variables, and patient terms fitted as random effects. A follow-up x load adjustment method interaction will be fitted; if this is not statistically significant at the 10% level overall treatment effects for follow-up and adjustment method will be reported. If the interaction is statistically significant differences in load between adjustment methods with and without follow-up will be described.

4.4.4 Model assumptions

For all methods outlined underlying assumptions will be checked using standard methods, e.g., residual plots, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses and comments made in footnotes. Sensitivity analyses may be performed to examine the effect on the study's conclusions of excluding outlying observations.

4.5 General content

4.5.1 Participant flow

The CONSORT flow diagram will be used to summarise the flow of participants through screening until follow-up throughout the course of the study (see Figure A1).

Protocol deviations defined in section 0 will be summarised by treatment group. The number of withdrawals of consent will be presented, along with reasons for withdrawal.

4.5.2 Baseline data

Baseline data (i.e. patient demography) will be described by treatment group and separately by surgical specialty for participants in the ITT analysis population. The thoracic and abdominal surgical specialties will be combined into one non-cardiac speciality as there were too few participants recruited in the thoracic specialty when the trial was halted.

Continuous variables will be summarised using the mean and standard deviation (SD) (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number (n/N) and percentage.

Any imbalances in the characteristics of the participants at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

4.5.3 Intervention

The intervention adherence will be described by surgical specialty (cardiac and non-cardiac surgery)

4.5.4 Harms

Adverse events will be summarised by MedDRA system organ class. Furthermore, adverse events and serious adverse events collected throughout the trial will be tabulated.

4.5.5 Subgroup analyses

The following subgroup analyses were planned:

- by surgical specialty (as described in section 7.1.2);
- by ARISCAT score (26-44 vs. ≥45);
- according to whether patients were receiving an additional prehabilitation programme as part of usual care at their hospital.
- according to nutritional status at baseline (MUST score 0 vs MUST score >=1 and <2 vs MUST score> 2)
- according to physical activity status at baseline (DASI score <=median vs DASI score > median)
- according to depression/anxiety status at baseline (HADS score <=7 vs HADS score >7)

As the trial was halted early, these subgroup analyses planned in the protocol will not be performed. The primary outcome and progression of training load (secondary outcome) will be described by allocation within the subgroups for surgical specialty (cardiac vs. non-cardiac) and ATISCAT score (26-44 vs. ≥45).

4.5.6 Further exploratory analyses

None

4.6 Missing data and outliers

A thorough data cleaning process will be carried out and attempts will be made to obtain any missing data by chasing until it is either received, confirmed as not available, or the study is at the analysis stage.

In all tables missing data for continuous variables will be indicated by footnotes. If the amount of missing data differs substantially between treatment groups potential reasons will be explored. The following strategy will only be applied to the primary outcome of the main study.

- If the proportion of missing data is less than 5% then complete case analysis will be performed (i.e., excluding cases with missing data).

- If the proportion of missing data is above 5% multiple imputation methods will be considered. A general imputation model that uses an iterative procedure to generate imputed values will be used to generate multiple complete data sets (e.g., using Stata's mi impute). The model of interest will be the fitted to each of the complete data sets and effect estimates combined using Rubin's rules. If appropriate, methods such as predictive mean matching will be used in order to ensure that imputed values lie within specific ranges.

5. References

Prospective External Validation of a Predictive Score for Postoperative Pulmonary Complications Anesthes. 2014;121(2):219-231. doi:10.1097/ALN.0000000000000334

Bang H, Ni L, Davis CE. Assessment of blinding in clinical trials. Control Clin Trials. 2004;25(2):143-56. Epub 2004/03/17

Connor KM, Davidson JR: **Development of a new resilience scale: the Connor-Davidson Resilience Scale (CD-RISC)**. *Depression and anxiety* 2003, **18**(2):76-82.
Lorig KR, Sobel DS, Ritter PL, Laurent D, Hobbs M: **Effect of a self-management program on patients with chronic disease**. *Effective clinical practice : ECP* 2001, **4**(6):256-262.

Hlatky MA, Boineau RE, Higginbotham MB, Lee KL, Mark DB, Califf RM, Cobb FR, Pryor DB. A brief self-administered questionnaire to determine functional capacity (the Duke Activity Status Index). Am J Cardiol. 1989 Sep 15;64(10):651-4. doi: 10.1016/0002-9149(89)90496-7. PMID: 2782256.

https://decisionaid.ohri.ca/eval_self.html

6. Glossary

Acronym	Details
AE	Adverse event
ARISCAT	Assess respiratory risk in surgical patients in Catalonia
CI	Confidence interval
CRF	Case report form
DSMC	Data safety monitoring committee
GMR	Geometric mean ratio
HR	Hazard ratio
ICH-GCP	International conference for harmonisation of good clinical practice
IQR	Inter quartile range
ITT	Intention to treat
MDT	Multidisciplinary team
MedDRA	Medical dictionary for regulatory activities
MIP	Maximal inspiratory pressure
PIL	Patient information leaflet
RCT	Randomised controlled trial
SAE	Serious adverse event

SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure

7. Revision history

Version 1.0 of the SAP should be signed off by relevant personnel before any data analysis is carried out. If changes need to be made to v1.0 before this time, possibly due to emerging methodologies, these changes should be documented in Table 1 below, with new version number, date and a summary of the changes with justification(s). If any changes to the methodologies are required after data analysis has begun, these should be documented in the final analysis report in a chronological manner, documenting all decisions made and their justification(s).

Table 1 SAP revision history

Version number	Revision date	Justification for revision

APPENDIX A: Skeleton tables and figures

The following summarises the planned outputs:

Section	Outputs	
Section 1 **Population**	**Tables and figures detailing study population**	
	Figure A1	Flow of participants
	Figure A2	Predicted and actual recruitment
	Table A3	Screening details
	Table A4	Withdrawals
Section 2 **Baseline, randomisation and surgical data**	**Summary tables of demographic and surgical information**	
	Table A5	Baseline demographic and clinical characteristics
	Table A6	Other baseline data
	Table A7	Day of surgery clinical measures and operative details
	Table A8	Protocol deviations
	Table A9	Randomisation and intervention timings
Section 3 **Primary and secondary outcome data, and adverse events**	**Summary data and treatment estimates for primary and secondary outcomes**	
	Table A10	SWAT primary and secondary outcomes
	Table A11	Primary and secondary outcomes
	Table A12	PPC and progression in training load, within surgical specialty and ARISCAT score
	Table A12	Adverse events and serious adverse events– in hospital
	Table A13	Adverse events and serious adverse events -during follow-up

Section 1: Population

Figure A1: Patient flowchart

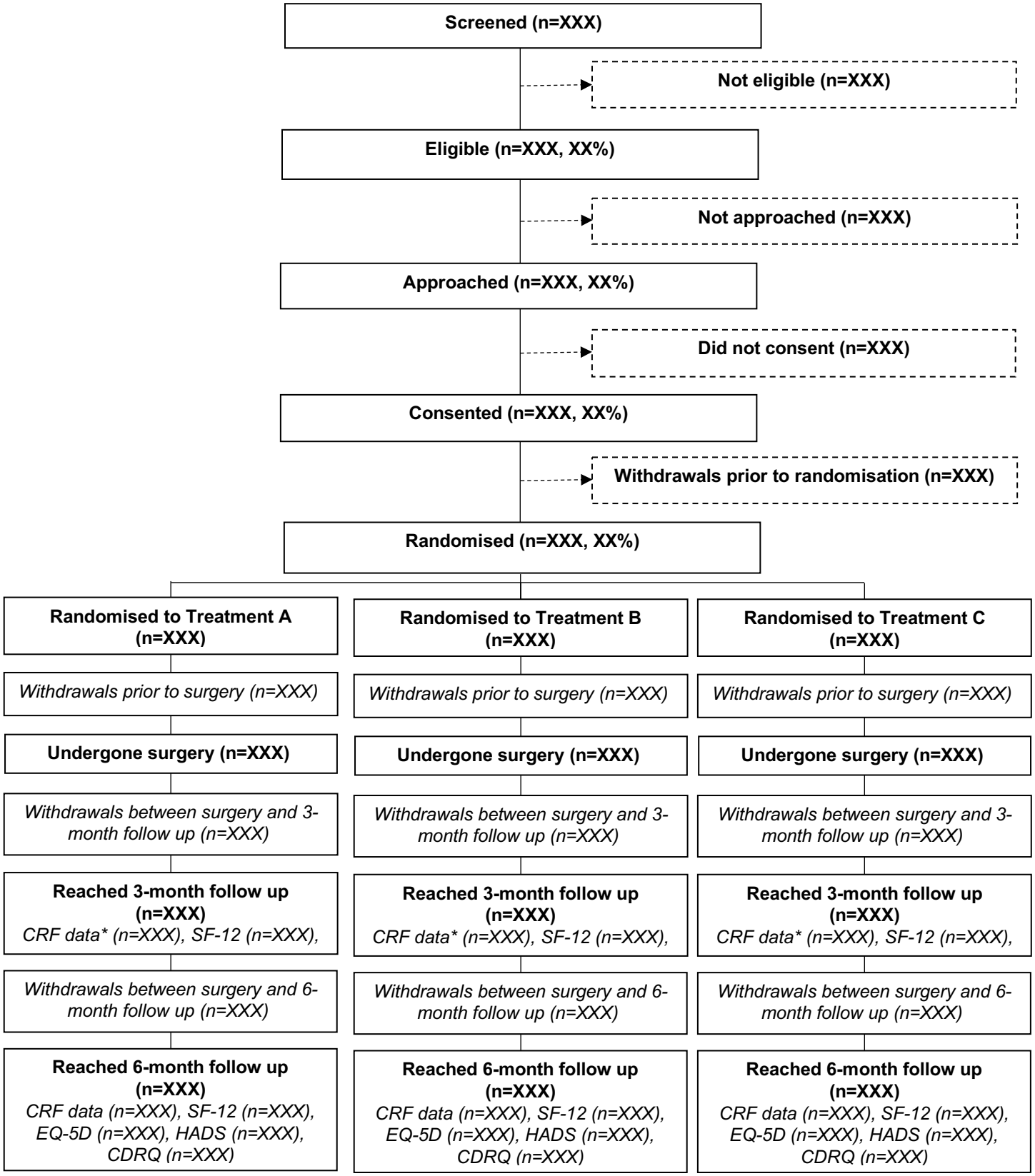


Figure A1: Predicted and actual recruitment

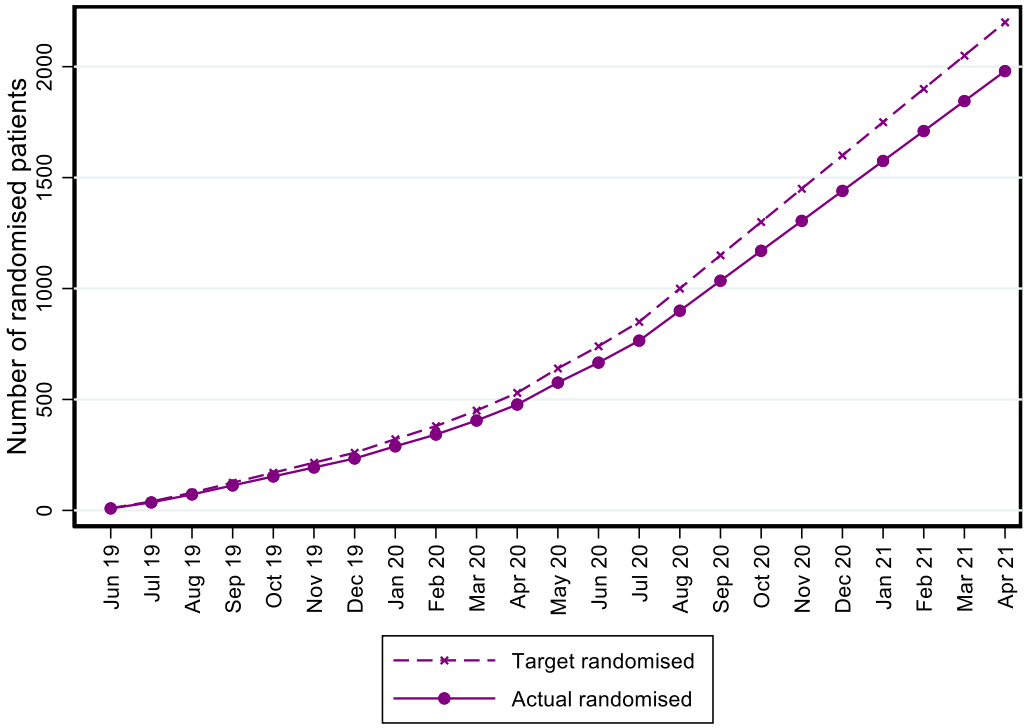


Table A3: Screening details

	Cardiac		Non-cardiac		Overall	
Reasons for ineligibility	**n**	**%**	**n**	**%**	**n**	**%**
<18 years of age						
Undergoing emergency surgery						
Not having elective major cardiac, thoracic or abdominal surgery						
ARISCAT score <26						
<14 days until planned operation date						
Unable to provide informed consent						
Unable to participate in the intervention						
Recent cardiac, thoracic or open abdominal surgery (in previous two months)						
Prisoners						
History of spontaneous pneumothorax						
Eardrum perforation within previous six weeks						
Phrenic nerve palsy						

Table A4: Details of withdrawals

Centre	Specialty	Timing of withdrawal	Reason for withdrawal

Section 2: Baseline and surgical data

Table A5: Baseline demography

		Treatment A (n=XXX)		Treatment B (n=XXX)		Treatment C (n=XXX)		Overall (n=XXX)	
		n	%	n	%	n	%	n	%
BASELINE CHARACTERISTICS									
Sex	Females								
Age – mean (SD)									
BMI – mean (SD)									
Ethnicity	White or Caucasian Black/Black British Mixed/Multiple ethnic groups Asian/Asian British Other ethnic group								
Type of surgery	Cardiac Thoracic Abdominal								
GENERAL COMORBIDITIES									
Diabetes	No Insulin Oral Diet								
Ischaemic heart disease									
Myocardial infarction within 6 months									
Heart failure									
Hypertension requiring treatment									
Peripheral vascular disease									
Stroke									
TIA									
Liver disease (exc cirrhosis)									
Cirrhosis									

		Treatment A (n=XXX)		Treatment B (n=XXX)		Treatment C (n=XXX)		Overall (n=XXX)	
		n	%	n	%	n	%	n	%
Renal disease	Stage 1 Stage 2 Stage 3a Stage3b Stage 4 Stage 5								
Condition associated with immunosuppression Immunosuppressant drugs Long-term steroids Oral steroids in previous 6 months									
RESPIRATORY COMORBIDITIES									
Asthma If yes, any hospital admissions in last 6 months									
Chronic pulmonary disease If yes, any hospital admissions in last 6 months									
Interstitial lung disease If yes, any hospital admissions in last 6 months									
Pulmonary hypertension If yes, any hospital admissions in last 6 months									
Bronchiectasis If yes, any hospital admissions in last 6 months									
Obstructive sleep apnoea If yes, any hospital admissions in last 6 months									
If yes, CPAP? If yes, any hospital admissions in last 6 months									
COVID-19 (test confirmed) If yes, any hospital admissions in last 6 months									
SMOKING STATUS									
Smoking	Non-smoker Ex-smoker >3 months								

		Treatment A (n=XXX)		Treatment B (n=XXX)		Treatment C (n=XXX)		Overall (n=XXX)	
		n	%	n	%	n	%	n	%
	Ex-smoker <3mths >14days Current smoker								
Number of years patient has smoked									
Number of cigarettes per day									
Number of cigars per day									
Number of pipes per day									
Number of “other” per day									
E-cigarettes									
CANCER / MALIGNANCY									
Surgery for cancer									
Primary or secondary tumour	Primary Secondary								
Site of malignancy	Lung Oesophagus Stomach Colon Rectum Anus Gall bladder Biliary tree Pancreas Liver Kidney Bladder Endometrium/Ovary Other								
Curative or palliative	Curative Palliative Don't know								

	Treatment A (n=XXX)		Treatment B (n=XXX)		Treatment C (n=XXX)		Overall (n=XXX)	
	n	%	n	%	n	%	n	%
Neo-adjuvant treatment in 6 months If yes, radiotherapy If yes, chemotherapy If yes, immunotherapy								
ARISCAT								
ARISCAT score – median (IQR) 26-44 >44								
Receiving an additional prehabilitation programme as part of usual care								
Nutritional status MUST score 0 MUST score 1-2 MUST score >2								

Table to be repeated with participants grouped by surgical specialty (cardiac vs non-cardiac) and grouped by SWAT randomised allocation

Table A6: Baseline questionnaires

		Treatment A	Treatment B	Overall
BASELINE QUESTIONNAIRES				
EQ-5D	Median (IQR) score			
SF-12	Median (IQR) score			
HADS	Median (IQR) score			
CRQ	Median (IQR) score			
Self-efficiency	Median (IQR) score			
DASI	Median (IQR) score			

Note instruments provide more than one summary score, table is for illustrative purposes

Table A7: Day of surgery clinical measures and operative details

		Treatment A (n=XXX)		Treatment B (n=XXX)		Treatment C (n=XXX)		Overall (n=XXX)	
		n	%	n	%	n	%	n	%
DAY OF SURGERY									
ROUTINE CLINICAL MEASURES									
Pre-operative SpO2 on admission									
Prescribed an antibiotic for a respiratory infection									
BLOOD TEST RESULTS									
Haemoglobin									
eGFR									
Creatinine									
Albumin									
ASA PHYSICAL STATUS CLASSIFICATION SYSTEM									
ASA score									
OPERATION DETAILS									
Open									
Laparoscopic / Minimally invasive									
OPCS code									
Primary incision made	Intrathoracic								
	Abdominal								
	Peripheral								
Estimated blood loss									
INTRAOPERATIVE VENTILATION									
Maximum positive end expiratory pressure (PEEP)									
Maximum tidal volume (SetTV)									
Maximum FiO2 intraoperatively (excluding during induction)									

Died in theatre

Table A8: Protocol deviations

	Cardiac		Non-cardiac		Overall	
	n	%	n	%	n	%
Non-adherence to the intervention						
Intervention not delivered per protocol						
Less than 2 weeks IMT training						
More than 8 weeks IMT training						
Missed all training						
More training than recommended (>2x 15min sessions/d)						
Continue training after surgery						
Not training at the recommended intensity (high resistance IMT group only)						
Other monitoring of study intervention						
Undergone surgery prior to completing the intervention						
Surgery delayed because of intervention						
Other non-compliance						
Ineligible but randomised						
Did not receive allocated intervention (cross-over)						

Table to be repeated with participants grouped by randomised allocation

Table A9: Details on randomisation and intervention timings

	Cardiac		Non-cardiac		Overall	
	n	%	n	%	n	%
Days between randomisation and surgery (Median, IQR)						

Table to be repeated with participants grouped by randomised allocation

Section 3: Primary and secondary outcomes

Table A10: SWAT primary and secondary outcomes

		Automatic load + Additional visit (n=XX)	Manual load + Additional visit (n=XX)	Automatic load + No additional visit (n=XX)	Manual load + No additional visit (n=XX)
PRIMARY OUTCOME					
Training load	Baseline				
	Day of surgery*				
	Change from baseline				
SECONDARY OUTCOMES					
Work	Baseline				
	Day of surgery*				
	Change from baseline				
MIP	Baseline				
	Day of surgery				
	Change from baseline				
FEV_1	Baseline				
	Day of surgery				
	Change from baseline				
FVC	Baseline				
	Day of surgery				
	Change from baseline				

Proportion of participants following at least 80% of the planned training sessions
Recorded on patient diary
Recorded on KHP2 device
Proportion of participants training at the prescribed intensity score of (RPE rating)
First, second and last line of patients diary
Most recent 10 sessions at additional visit (participants randomised to additional visit only)

***** Measurement taken from last line of patients diary. This was on day of surgery for XX participants, within 2 days of surgery for XX participants, within 3-7 days for XX participants and within >7 days for XX participants

Table A11: Primary and secondary outcomes

Outcome	Randomised to IMT (n=xx)	Randomised to Sham IMT/Usual care (n=xx)	Randomised to Sham IMT (n=xx)	Randomised to usual care (n=xx)	Effect (95% CI)*	p-value
Any PPC					RD/RR	
Respiratory infection					-	-
Respiratory failure					-	-
Pleural effusion					-	-
Atelectasis					-	-
Pneumothorax					-	-
Bronchospasm						
Aspiration pneumonitis					-	-
Invasive ventilation					-	-

Non-invasive ventilation (including continuous positive airway pressure (CPAP) and/or pressure support (BIPAP))	-	-
Optiflow (highflownasaloxygentherapy)	-	-
Prophylactically to prevent a pulmonary complication	-	-
For treatment of a pulmonary complication	-	-
Length of ICU stay	-	-
Length of hospital stay	-	-
Antibiotic prescription	-	-
Bronchodilator prescription	-	-
Change in maximal inspiratory pressure (MIP)	-	-
Change in Spirometry (forced expiratory volume, FEV1 and forced vital capacity, FVC) measurements	-	-
Progression in training load		
In-hospital mortality	-	-
30-day mortality	-	-
Patient questionnaires at 3 months	-	-
Patient questionnaires at 6 months	-	-

* Effect estimate is from model comparing high resistance IMT to the sham IMT and usual care groups combined

Table A12: PPC and progression in training load, within surgical specialty and ARISCAT score

Outcome	Randomised to IMT (n=xx)	Randomised to Sham IMT/Usual care (n=xx)
By surgical specialty		
Any PPC		
Cardiac (n=XXX)		
Non-cardiac (n=XXX)		
Progression in training load		
Cardiac (n=XXX)		
Non-cardiac (n=XXX)		
By ARISCAT score		
Any PPC		
Score 24-44 (n=XXX)		
Score ≥45 (n=XXX)		
Progression in training load		
Score 24-44 (n=XXX)		
Score ≥45 (n=XXX)		

Table A13: Adverse events and serious adverse events during index hospital admission

	Randomised Patients (N=XXX) AEs		SAEs		Relatedness (SAEs)					Intensity (SAEs) *Unanticipated events only*		
	Events/ Patients	%[1]	Events/ Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Any anticipated event												
Infective												
Viral Infection												
Pneumonia												
Respiratory infection												
….												
Cardiovascular												
….												
GI												
….												
Respiratory/pulmonary												
….												
Nervous system / Neurological / Psychiatric												
…												
Immune system												
…												
Metabolism / Nutrition												
…												
Eye												
…												

	Randomised Patients (N=XXX)				Relatedness (SAEs)					Intensity (SAEs) *Unanticipated events only*		
	AEs		SAEs									
	Events/ Patients	%[1]	Events/ Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Ear / Labyrinth												
…												
Hepatobiliary												
…												
Renal / Urinary												
…												
Reproductive / Breast												
…												
Skin / Subcutaneous tissue												
…												
Musculoskeletal / Connective tissue / bone												
…												
General												
…												
Anatomical / Surgical dam												
…												
Oncology												
…												
Investigations												
…												
Injury												
…												

	Randomised Patients (N=XXX) AEs		SAEs		Relatedness (SAEs)					Intensity (SAEs) *Unanticipated events only*		
	Events/ Patients	%[1]	Events/ Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Re-operation												
…												
Chemo / Radio												
…												
Any event not anticipated												
…												

Table of events (excluding relatedness and intensity) to be repeated with participants grouped by treatment received

Table A14: Adverse events reported at 3 and 6 month follow-up

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Any anticipated event										
Infective										
….										
Cardiovascular										
….										
GI										
….										
Respiratory/pulmonary										
….										
Nervous system / Neurological / Psychiatric										
…										
Immune system										
…										
Metabolism / Nutrition										
…										
Eye										
…										
Ear / Labyrinth										
…										
Hepatobiliary										
…										

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Renal / Urinary										
…										
Reproductive / Breast										
…										
Skin / Subcutaneous tissue										
…										
Musculoskeletal / Connective tissue / bone										
…										
General										
…										
Anatomical / Surgical dam										
…										
Oncology										
…										
Investigations										
…										
Injury										
…										
Re-operation										
…										
Chemo / Radiotherapy										
…										
Any event not anticipated										

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
...										

Table of events (excluding relatedness and intensity) to be repeated with participants grouped by treatment received

Table A15: Serious adverse events reported throughout the trial

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Any anticipated event										
Infective										
….										
Cardiovascular										
….										
GI										
….										
Respiratory/pulmonary										
….										
Nervous system / Neurological / Psychiatric										
…										
Immune system										
…										
Metabolism / Nutrition										
…										
Eye										
…										
Ear / Labyrinth										
…										
Hepatobiliary										
…										

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
Renal / Urinary										
…										
Reproductive / Breast										
…										
Skin / Subcutaneous tissue										
…										
Musculoskeletal / Connective tissue / bone										
…										
General										
…										
Anatomical / Surgical dam										
…										
Oncology										
…										
Investigations										
…										
Injury										
…										
Re-operation										
…										
Chemo / Radiotherapy										
…										
Any event not anticipated										

	Randomised patients (n=XX)		Relatedness					Intensity (*Unanticipated events only*)		
	Event Patients	%[1]	Not related	Unlikely to be related	Possibly related	Probably related	Definitely related	Mild	Moderate	Severe
…										