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

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Glossary / abbreviations

AE	Adverse event - any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.
AKI	Acute kidney injury - an acute increase in serum creatinine > 26.4 µmol/l or a percentage increase in serum creatinine of more than or equal to 50%
AR	Adverse reaction – any undesirable experience that has happened a subject while taking a drug that is suspected to be caused by the drug or drugs
ARDS	Acute respiratory distress syndrome
ARISCAT	Assess Respiratory Risk in Surgical Patients in Catalonia
BRU	Biomedical Research Unit
BTC	Bristol Trials Centre
CDRQ	Connor Davidson Resilience Questionnaire
CI	Chief Investigator
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure – a method of respiratory ventilation providing oxygen for any period of time post extubation
CPET	Cardiopulmonary exercise testing
CRF	Case report form
CSG	Clinical Studies Group
CTEU	Clinical Trials and Evaluation Unit
DASI	Duke Activity Status Index
DMSC	Data monitoring and safety committee
DVT	Deep Vein Thrombosis
FEV_1	Forced expiratory volume
FVC	Forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HADS	Hospital Anxiety and Depression Scale
HRA	Health research Authority
HRQOL	Health-Related Quality of Life
HTA	Health technology Association
IABP	Intra-aortic balloon pump
ICH-GCP	International conference for harmonisation of good clinical practice
ICU	Intensive care unit
IMD	Index of Multiple Deprivation
IMT	Inspiratory muscle training
ITT	Intention to Treat
MDT	Multi-disciplinary team
MHRA	Medicines and healthcare products regulatory agency
MI	Myocardial infarction
MIP	Maximal inspiratory pressure
MUST	Malnutrition Universal Screening Tool
NHS	National Health Service
NGAL	Neutrophil gelatinase associated lipocalin – a specific marker of acute kidney injury
NIAA	National Institute of Academic Anaesthesia
NICE	National Institute for Health & Care Excellence
NIHR	National Institute for Health Research

NIV	Non-invasive ventilation
PCPIE	Patient, carer and public involvement engagement
PE	Pulmonary embolus
PI	Principal Investigator
PIL	Patient information leaflet
PONS	Peri-operative Nutrition Screen
PPC	Postoperative pulmonary complications
PPI	Patient Public Involvement
POA	Pre-operative assessment
QALY	Quality adjusted life years
QRI	QuinteT Recruitment Intervention
QuinteT	Qualitative Research Integrated within Trials
RCT	Randomised controlled trial
REC	Research ethics committee
Residual volume	Volume of air left in the lungs at the end of a maximal expiration
RPE	Rate of perceived exertion
RRT	Renal replacement therapy
SAE	Serious adverse event - events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.
SF-12	Short Form-12 questionnaire
SIV	Site initiation visit
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
StEP-COMPAC	Standardising endpoints in perioperative trials- Core outcome measures in perioperative and anaesthetic care
SUSAR	Suspected unexpected serious adverse reaction - an untoward medical occurrence suspected to be related to a medicinal product that is not consistent with the applicable product information and is serious.
SWAT	Study within a trial
TIA	Transient ischemic attack
TMG	Trial management group
TSC	Trial steering committee
UH Bristol	University Hospitals Bristol NHS Foundation Trust

1. Trial summary

After major operations, some patients develop complications of the lungs, including pneumonia. These complications can be serious and may result in long stays in hospital, admission to intensive care and even death. They also prolong recovery from surgery and reduce patients' quality of life. In the long term, lung complications increase the risk of poor health and even death for up to ten years after surgery. Poor health due to lung complications also increases healthcare costs. Lung complications are common, affecting on average one in ten patients. The risk for a particular individual depends on their current health and the type of surgery they are having. Consequently, trying to prevent lung complications is important for patients and the National Health Service (NHS).

Inspiratory muscle training (IMT) is a package of breathing exercises designed to improve the strength and endurance of the muscles in the chest that control breathing. IMT involves breathing in and out through a hand held device that imposes a resistance, making breathing 'more strenuous' than normal. IMT is safe and applies the well-established principles of muscle resistance training, so can be likened to 'lifting a weight'. IMT needs to be done for about 15 minutes twice per day and can be performed at home whilst seated.

Recent studies have suggested that performing IMT twice per day for as little as two weeks before an operation might halve the risk of lung complications. Unfortunately, the benefits of IMT remain uncertain, because the previous studies recruited too few patients and many were not designed or carried out well.

The INSPIRE study will be large, to find out once and for all whether IMT reduces lung complications in patients at high-risk of having lung complications, for example, patients who are older, have anaemia, and are having an operation that takes more than 2 hours to perform. We will invite all adult patients having operations in the chest or abdomen under general anaesthesia who have a high risk of lung complications to take part. We will randomly assign participants to one of three different types of breathing exercises (two of these will use an IMT device and one will not) in the period leading up to the operation.

1. **High resistance IMT.** Participants will be given a device and taught to do the IMT using the hand held device and instructed to train twice per day (30 breaths each time) for a minimum of two weeks. Participants will be taught to increase the load resistance on their device based on their breathing effort which they will self-assess using a scale. If they have a longer wait, they can continue doing the exercises until the operation.

2. **Low resistance IMT.** Participants will do the same as for the high intensity group, but the device will be set to a training load that will not change the strength or endurance of the inspiratory muscles. It is important that participants in this group believe that they are actually training, as the aim of this group is to account for any "placebo" effect, thereby ensuring that any reduction in lung complications in the high intensity group is "real".

3. **Usual care.** Participants will be given advice about the importance of deep breathing exercises and a leaflet instructing them how to do these exercises, but will otherwise have no additional breathing training before surgery.

The clinical team looking after patients at the time of surgery will not know to which group a patient has been allocated. We will measure the strength of the inspiratory breath when a

patient agrees to take part and immediately before the operation in all three groups, so that we can determine which type of breathing exercises work. In the high and low resistance IMT groups, we will monitor how much training patients were able to complete in the two weeks prior to surgery by asking them to complete a diary of their training (the number of training sessions and duration of each session is recorded automatically on the device).

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 face-to-face meeting; (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. The study will be supported by an integrated QuinteT Recruitment Intervention (QRI) for 18 months.

2. Background

2.1 Postoperative pulmonary complications (PPCs) after major surgery

Postoperative pulmonary complications affect between 2% and 40% of patients undergoing cardiac, thoracic and abdominal surgery [1, 2]. PPCs markedly increase the risk of death within 30 days of surgery (from 2.5% in patients without PPCs to 18% in patients with PPCs) [3] and have a detrimental effect on both early and late health related quality of life (HRQoL) [4]. PPCs also increase postoperative length of stay (by 6-8 days) [5], ICU admissions, hospital readmissions, and costs (which are 12-fold higher in those with PPCs) [5]. Importantly, post-
2.2 operative complications have long-term health implications and may reduce long-term survival [3, 6].

Inspiratory muscle training (IMT)

Inspiratory muscle training (IMT) is a breathing intervention to improve the strength and endurance of the inspiratory muscles, the diaphragm, intercostal and other accessory muscles. IMT involves breathing in and out through an inexpensive, hand held device that imposes a resistance, making breathing more strenuous than normal, to improve the strength and endurance of the inspiratory muscles.

There is some evidence that IMT undertaken before surgery improves pulmonary function and reduces the incidence of PPCs. As little as two weeks of IMT has been shown to improve: an index describing inspiratory muscle strength (maximal inspiratory pressure (MIP)) [7], diaphragm thickness [8], inspiratory muscle strength [9] and endurance [10]; it also has been shown to ameliorate postoperative decline in maximal inspiratory pressure (MIP) [11]. IMT has

been used with beneficial effect in a variety of patient populations, including surgical patients [12], patients with chronic obstructive pulmonary disease (COPD) [13], stroke [14], heart failure [15] asthma [16] and cystic fibrosis [17]. IMT is a relatively inexpensive intervention that can be undertaken in the patient's own home in a sitting or recumbent position. This makes it an attractive option for many surgical patients who may be unable or unwilling to do physical exercise before surgery. Thus, if effective, perioperative IMT would improve patient health by reducing complications and potentially improving HRQoL. However, uptake in the NHS is currently very limited, in part due to scepticism about the quality of the evidence base.

Evidence for the efficacy of IMT in patients undergoing major surgery

2.3 To date, there are four published systematic reviews and meta analyses that investigated the effectiveness of IMT on PPCs and length of hospital stay [12, 18-20] in surgical patients. One focused on cardiac surgery only (8 randomised controlled trials (RCTs), 4 preoperative IMT and 4 pre- and postoperative IMT) [18], one on cardiac and major abdominal surgery (12 RCTs, pre-operative IMT only) [12], and two on cardiac, thoracic and abdominal surgery (17 RCTs, 13 preoperative IMT, 2 postoperative IMT and 2 pre- and postoperative); 8 RCTs, preoperative IMT only including quasi-randomised trials, respectively) [19, 20]. All meta analyses found significantly decreased relative risks (RR) of any or specific PPCs with IMT, ranging from 0.45 to 0.6: RR 0.6, 95% CI 0.5-0.8 (any PPC, 386 patients) [18]; RR 0.53, 95% CI 0.34-0.83 (atelectasis, 443 patients) and RR 0.45, 95% CI 0.26-0.77 (pneumonia 675 patients) [12]; RR 0.50, 95% CI 0.39-0.64 (666 patients) [19]; RR 0.48, 95% CI 0.26-0.89 (249 patients) [19]. Although the effect size appears highly beneficial, the majority of RCTs included in the above meta-analyses were small (<100 participants) and none of the RCTs were blinded. Most were at high or unclear risk of bias in at least one domain, and over half were at high or unclear risk of allocation bias due to unconcealed randomisation. Therefore, despite some evidence that IMT can reduce PPCs after surgery, in order to change practice the intervention needs to be assessed in an adequately powered high quality trial with patient masking (blinding).

2.4

Mode of delivery of high resistance IMT

The *delivery* of IMT varies considerably in the published RCTs [12, 18-20]. Most researchers have implemented daily or at least weekly face-to-face meetings (hospital visits by patients or home visits by the physiotherapist) to ensure that participants are using the correct training technique and intensity [12]. RCTs with closer supervision showed a greater treatment effect [12]. Close supervision allows the resistance that a participant uses during training to be adjusted so that the perceived exertion remains constant as improvements in function are achieved, leading to robust improvements in inspiratory muscle function [21]. Progression of the training intensity is essential in order to maintain muscle 'overload', thereby creating the stimulus for training adaptations [22]. It is especially important to ensure that patients train at an adequate intensity during short interventions (such as during the pre-operative period), since muscle adaptations to training exhibit a dose-response relationship [22].

It may not be feasible to deliver a closely supervised intervention in usual care, across the NHS, even if the trial were to show such an intervention to be effective and cost effective. The only study to implement a pragmatic intervention was the recently published RCT by Valkenet et al. [23], in which 120 patients with oesophageal cancer were randomised to a home-based IMT intervention (minimum 2 weeks before surgery) or usual care. In this study, all patients in the IMT group received one baseline face-to-face IMT training session and then continued training at home on their own. The physiotherapist contacted them by telephone after 3 days and if the

training had not been undertaken as instructed, a follow-up appointment was made at an outpatient clinic to repeat the face-to-face training and adjust the training load. In this study, only 54% of patients completed ≥80% of the prescribed training sessions and only 40% of all sessions were completed at the prescribed intensity. The main factor that prevented training at the prescribed intensity was that patients found it difficult to increase the load on their device so that training could be undertaken at the correct intensity. This was despite the fact that appropriate training and instructions were provided and patients were offered telephone support. We will therefore use the pilot phase of the trial (Phase 1) to determine the optimal way to deliver the intervention to optimise / maximise the inspiratory training effort. We will test whether an additional face-to-face meeting with the research nurse/physiotherapist to monitor progress results in "better" training (i.e. more patients progressing their training load). We will also test whether using the automatic load function on the IMT device to increase training load automatically (as opposed to patients increasing the training load manually).

3. Rationale

Increasingly, participants referred for surgery are older, less healthy, and have co-morbidities, putting them at high risk of post-operative morbidity and mortality related to PPCs. IMT is a simple and inexpensive inspiratory muscle training method that may reduce PPCs related to surgery, but its effectiveness requires further assessment in an adequately powered, pragmatic, good quality trial.

4. Aims and objectives

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

Specific objectives are to estimate:

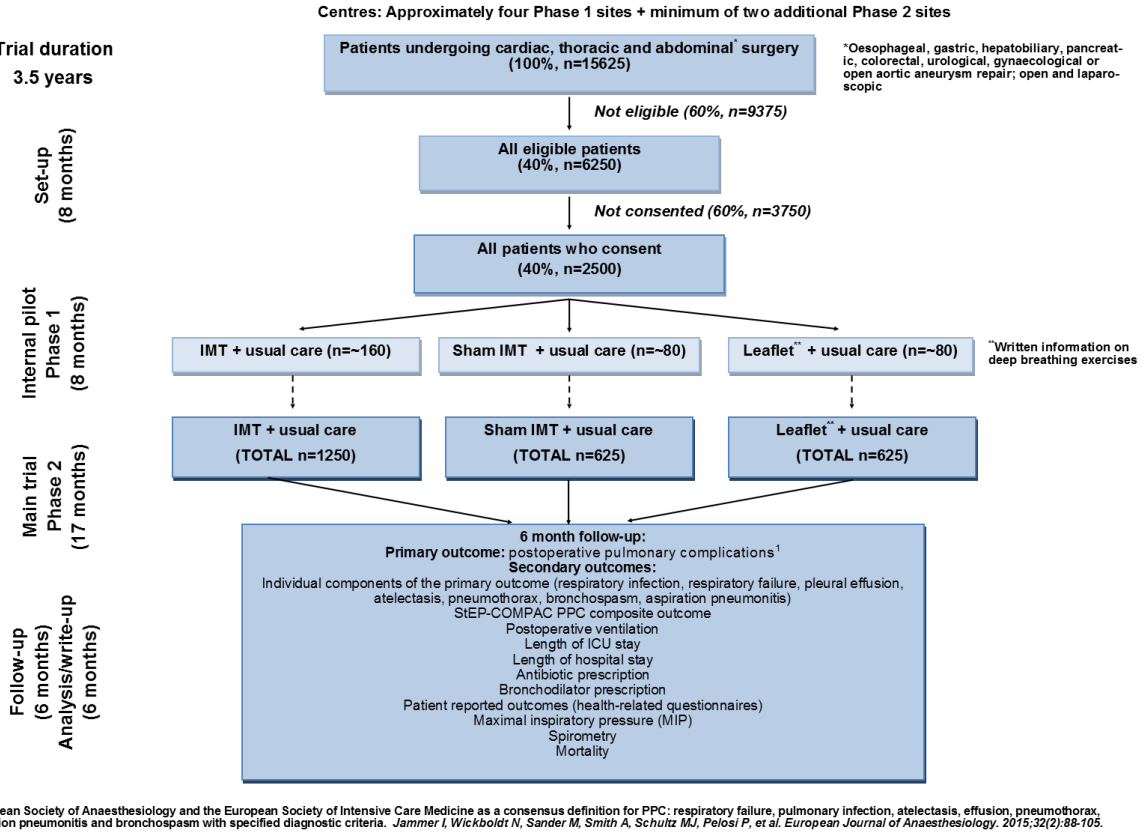
A. The optimal mode of delivery for the IMT intervention;
B. The difference between groups in the incidence of PPCs after surgery;
C. The difference between groups with respect to a range of secondary outcomes including: individual components of the primary outcome; postoperative ventilation; length of intensive care unit (ICU) stay; ; length of hospital stay; antibiotic prescription; bronchodilator prescription; HRQoL; maximal inspiratory pressure (MIP), spirometry (forced expiratory volume, FEV_1 and forced vital capacity, FVC) and mortality;
D. The cost effectiveness of IMT compared to usual care.

The QuinteT (Qualitative Research Integrated within Trials) Recruitment Intervention (QRI) is integrated into the first phase of study recruitment. The QRI will identify, describe and understand barriers to optimal recruitment, and provide potential solutions to address these barriers [24] (section 5.2.5 Integrated qualitative research

5. Plan of Investigation

Study schema

5.1



[1] European Society of Anaesthesiology and the European Society of Intensive Care Medicine as a consensus definition for PPC: respiratory failure, pulmonary infection, atelectasis, effusion, pneumothorax, aspiration pneumonitis and bronchospasm with specified diagnostic criteria. *Jammer I, Wickboldt N, Sander M, Smith A, Schultz MJ, Pelosi P, et al. European Journal of Anaesthesiology. 2015;32(2):88-105.*

5.2

Study 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 [25, 26] 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).

5.2.1 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 face-to-face meeting (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 (section 5.2.2);

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 (section 5.2.2);

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.

5.2.2. 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 face-to-face meeting 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 face-to-face hospital visit	**AV**	**MV**
No additional face-to-face hospital visit	**AN**	**MN**

AV Automatic load adjustment and one additional face-to-face hospital visit;

MV Manual load adjustment and one additional face-to-face hospital visit;

AN Automatic load adjustment and no additional face-to-face visit;

MN Manual load adjustment and no additional face-to-face hospital visit.

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 face-to-face hospital visit vs no additional face-to-face hospital visit

i) One additional face-to-face hospital visit

Participants in the high resistance IMT group will attend an additional face-to-face hospital visit 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 watched a step-by-step digital recording (video) on how to use the device at the initial IMT training session and will have 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. Assessment of IMT technique and adherence will also be performed at routine pre-operative visits if any are scheduled.

ii) No additional face-to-face hospital visit

Participants will attend the initial IMT training session with a research nurse or physiotherapist but participants will not come back for the additional face-to-face hospital visit.

5.2.3 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 face-to-face visit in Phase 2 if the increase in training load from baseline in the no additional visit group is similar to that in the additional visit group. We will consider automatic load adjustment in Phase 2 if the increase 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 visit) 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 +/-
5.2.4 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.

5.2.5 Integrated qualitative research

Many RCTs are challenging for recruitment because of difficulties faced by recruiters in explaining and justifying concepts inherent in the design (such as randomisation and uncertainty) and in particular where one of the options is a 'sham' procedure. We will assess recruitment and retention in a two-stage integrated QRI to identify and address recruitment challenges [24].

QRI Stage 1: Understanding recruitment

A multi-faceted, flexible approach will be used to investigate site-specific or wider recruitment obstacles. This will comprise the following:

i) Mapping of eligibility and recruitment pathways: This will identify points in the recruitment pathway at which patients do not continue to the RCT, e.g. discussion of the study with the research nurse or surgeon.

ii) In-depth interviews: These will be conducted and audio-recorded with i) members of the Trial Management Group (n=3-5), (ii) clinicians or researchers involved in study recruitment, across each recruiting site and surgical specialty (n=12-20), and (iii) eligible patients who have been approached to take part in the study (n=5-20). Interviews provide data about the presentation of the study, application in clinical centres, and insights about recruitment barriers.

iii) Audio-recording of recruitment appointments: The recruitment appointment(s) where the study is presented and consent is sought for participation in the RCT will be audio-recorded with consent. These appointments will be analysed to identify recruitment difficulties, and provide the basis for feedback and/or training as required. Recordings will be sought from each discipline at each centre to ensure maximum variation.

iv) Study documentation: The QRI team will assist with the wording of patient information leaflets (PIL) and consent forms to prevent wording that is unclear or potentially open to misinterpretation.

QRI Stage 2: Feedback to Chief Investigator (CI) / Trial Steering Committee (TSC) and plan of action

The QRI researcher will present summaries of anonymised findings to the trial CI (and TSC, if agreed by CI), identifying factors that appear to be hindering recruitment with supporting evidence. A plan of action will then be drawn up to try to improve recruitment. It is likely that some aspects of the plan of action will be generic, such as how to explore patient preferences, as well as issues specific to the proposed trial that are modifiable.

The QRI has successfully identified common recruitment challenges [33] and we will apply this approach in the pilot stage to explore acceptability of the design both clinically, and with patients. In the main study we will closely monitor screening and recruitment data and use analysis of patient consultations to facilitate training for recruiters to maximise recruitment and information delivery.

The QRI has been presented as two distinct stages for clarity (section 6.3.6), although in reality these are likely to overlap. For instance, new avenues of enquiry will emerge throughout the conduct of the QRI (e.g. in feedback meetings), and rigorous monitoring of screening logs before/after interventions may indicate a need for further investigations (stage 1) or intervention (stage 2).

5.2.6 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
5.3 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.

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, or consultant with expertise in either IMT, perioperative medicine, or both) 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.

Key design features to minimise bias

Bias arising from the randomisation process

Concealed randomisation will protect against bias arising from the randomisation process [27]. We will stratify the allocation by centre and specialty to ensure balanced groups across study
5.4 arms within these strata.

5.4.1

Bias due to deviations from intended interventions

We aim to blind participants in the high and low resistance IMT groups to their allocation throughout their time in the study and will measure our success in doing this. If successful,
5.4.2 blinding of participants will prevent bias due to participants changing behaviours related to their health, contingent on knowledge of their allocation. Participants in the usual care group will know that they are training without a device; however, they will be given a leaflet with information on the importance of deep breathing exercises (this is part of usual care in some hospitals). They should therefore have no perception that they might be in an "inferior" group.

We also aim to blind research and clinical personnel involved in the follow-up of participants to all allocation throughout participants' time in the study and will measure our success in doing this. If successful, blinding of research personnel will prevent bias due to them changing how they manage participants clinical or interact with them, contingent on knowledge of their allocation.

Although it is difficult to achieve successful and complete blinding of participants, care providers and outcome assessors in a study of a lifestyle intervention, the inclusion of a low resistance IMT group is likely to blind participants with respect to their allocation to low and high IMT. Participants are unlikely to be familiar with IMT, since IMT is not a 'mainstream' intervention (for example, like physical activity), so they are unlikely to have expectations of benefit from being in one group rather than the other. The study will be presented to patients as a study of 'breathing exercises' before surgery. Some participants will have a device and others won't (they will get a leaflet with instructions on deep breathing exercises). This way of presenting the study will make it less likely that patients will seek information about the intervention they are receiving because of a prior knowledge of the interventions. Because the interventions will take place before hospital admission for surgery, it is likely that clinicians and other hospital staff caring for participants during their hospital stay will not be aware of participants' allocation. Participants will be advised where possible not to discuss their treatment allocation with clinicians, other hospital staff and research team members.

These features of the study will protect against bias due to deviations from the intended intervention. Members of the research team at the coordinating centre (apart from the statistician responsible for unblinded analyses and the IT developer responsible for the randomisation system) will also be blind to participants' allocation. The success of blinding will be assessed; in case participants in the low IMT group may become aware that they are not performing the real intervention and their care team may become unblinded if patients discuss their intervention. Bias will also be minimised by administering the interventions (high resistance IMT and low resistance IMT) and other procedures undertaken during the study according to standard protocols, and by pre-defining all procedures for participant follow-up and applying the procedures to all participants in the same way. We will monitor adherence to all aspects of the protocol.

Bias in measurement of the outcome

For the SWAT, maximal inspirational pressure will be measured objectively (recorded automatically by the POWERbreathe device).

5.4.3 For the main study, we will minimise the measurement of outcomes by providing clear unambiguous definitions for each outcome measure, blinding all individuals assessing outcomes (including participants with respect to patient-reported outcomes) and assessing the success of blinding of outcome assessors by asking them to "guess" which group they think patients were in (bang blinding index). Study participants will be unaware of the "true" difference between the interventions so we will not ask patients to "guess" which group they were in.

Bias due to missing outcome data

5.4.4 We will minimise attrition bias by: i) maintaining contact with participants throughout the duration of the study to maximise the proportion of participants for whom all outcome data are available and the proportion of participants who receive the intervention to which they were allocated; ii) implementing measures to promote adherence (e.g. appropriate training and telephone support); and iii) documenting non-adherence to allocated intervention. The data will also be analysed by intention to treat (ITT) (section 7.1).

In estimating the target sample size, we have not allowed for loss to follow-up as data on PPCs (primary outcome) are collected during the hospital stay and the follow-up period (for secondary outcomes) is short (6 months). We will however pay attention to keeping in touch with participants in order to maximise retention up to 6 months.

5.4.5 *Bias in selection of the reported result*

We will minimise reporting bias by having pre-specified outcomes and a pre-specified analysis plan.

5.5 Study population

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

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.

5.5.2 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

5.6 Study interventions

5.6.1

The POWERbreathe® KHP2 and KH2 devices

Participants in the high resistance and low resistance IMT groups will undertake a minimum 2-week IMT intervention using the POWERbreathe® KHP2 electronic training device (POWERbreathe International Ltd, Southam, Warwickshire, United Kingdom). The POWERbreathe® KHP2 device stores a patient's inspiratory flow rate, tidal volume, pressure, and power data electronically and can therefore quantify the patient's adherence to the IMT and training intensity objectively. The POWERbreathe® KHP2 device is reusable; valve heads can be sterilised and the valves are also replaceable.

Each site will have access to a POWERbreathe® KH2 device which will be used by participants in a clinical setting only, under the supervision of appropriately trained research nurses and/or physiotherapists. The POWERbreathe® KH2 device will be used to measure MIP accurately (the KHP2 devices given to patients estimates MIP, but cannot measure MIP directly). The POWERbreathe® KH2 device is reusable; valve heads can be sterilised and the valves are also replaceable.

Training research nurses/physiotherapists to deliver high resistance IMT or low resistance IMT

Research nurses and/or physiotherapists (ideally 1-2 at each participating site) will receive standardised training on how to perform a MIP measurement [28, 29] using the KH2 POWERbreathe® device (section 6.3.2), and how to instruct patients to perform IMT correctly
5.6.2 using the POWERbreathe® KHP2 device. Standardised literature will be distributed to all sites with a training video for reference. A member of the INSPIRE research team will visit each site to deliver face to face training at the start of the study.

High resistance IMT

5.6.3.1 Training participants in the high resistance IMT group

5.6.3 Participants enrolled in the high resistance IMT group will have an initial face to face meeting (lasting up to 1 hour) with a research nurse or physiotherapist who has received training in how to deliver the IMT intervention (section 5.6.2). Participants will have FEV_1 and FVC readings taken with a spirometer and MIP measured using the POWERbreathe® KH2 device before being shown how the POWERbreathe® KHP2 device works, how to remove and clean the valve, how to breathe in and out correctly using the device, how to record their perceived exertion using an RPE rating scale [30, 31] and how to complete the paper training diary. The paper training diary will also include a comments section.

Participants will watch a training video during the face-to-face meeting which will provide step-by-step guidance on the correct use of the KHP2 device and on how to increase the training load in response to the participant's perceived exertion using the RPE rating scale. Participants will also be given written instructions to take home.

During the face to face appointment participants will undertake a supervised training session with the research nurse or physiotherapist of as many breaths as can be tolerated up to a maximum of 30 breaths (section 5.6.3.2). Participants will be coached by the research nurse or physiotherapist to maximise tidal volume by exhaling and inhaling fully for every breath of the training session. In addition, they will be encouraged to breathe IN as rapidly as possible, and to breathe OUT in a relaxed manner. This approach will maximise the training stimulus delivered to the inspiratory muscles.

5.6.3.2 High resistance IMT training protocol

The mode of delivery of the high resistance IMT intervention in the main study will be contingent on the results of the SWAT with regards to the need for an additional face-to-face visit and manual vs. automatic load adjustment on the IMT device (section 5.2).

We will use a modified version of the IMT intervention protocol used in the recent study by Valkenet et al [23] (based on the protocol of Bailey et al [32]). Participants will undertake a maximum of 30 breaths (or as many breaths as can be tolerated), twice daily, 7 days per week, using the POWERbreathe® KHP2 at home. The initial training load for participants in the high intensity IMT arm will be set by the research nurse or physiotherapist at the first face-to-face meeting (section 5.6.3.1).

Training intensity will commence at 50% of MIP. If the patient cannot tolerate this, the load will be titrated to the maximum level that the patient can tolerate for at least 20 breaths (30 breaths is the maximum tolerable load) aiming for a starting workload of at least 40% of MIP. During the subsequent training intervention the load will be increased in accordance with tolerability quantified using rate of perceived exertion scale (a modified Borg exertion scale) which quantifies the perceived exertion of breathing from 0 to 10 ("How intense was the training session?") [30, 31]. Participants will refer to the RPE rating scale and rate their perceived exertion in their paper training diary after each training session.

Participants in Phase 1 who are randomised to the 'manual load adjustment' group will be given a table of pre-calculated training loads (Figure 3) to allow them to increase the load on their device by 5% if their perceived exertion at the end of a training session is 5 or less (using the RPE rating scale as shown in Figure 2).

Participants in Phase 1 who are randomised to the 'automatic load adjustment' group will be taught how to perform the first 3 test breaths using the IMT device which will automatically estimate MIP and adjust to the correct load. Participants in the 'automatic load adjustment' group will also record their perceived exertion using the RPE rating scale.

Participants in Phase 1 undertaking an additional face-to-face hospital visit within one week of starting IMT training will have MIP measured during the second visit using the POWERbreathe® KH2 device (ideally by the same person who performed the initial measurement), and their paper training diary and training load increments will be reviewed. Participants will undertake a supervised training session at this visit, during which their training technique will be reviewed and improved, as appropriate. Their perceived exertion rating (using the RPE scale) will be recorded immediately after this supervised session, and MIP will be recorded (pre- and post-training). Training data recorded by the POWERbreathe® KHP2 will also be extracted and recorded on the case report forms (CRF). The training load will be increased by 5% if any of the following conditions are met:

i) MIP has increased;
ii) the RPE rating is 5 or less at the additional visit;
iii) the RPE rating recorded in the paper training diary during any of the previous two training sessions was 5 or less.

Patients will be instructed to continue to increase the training load over the next week, in response to their rating.

All high resistance IMT participants will be given a usual care leaflet containing advice on deep breathing exercises.

5.6.4 Low resistance IMT

5.6.4.1 Training participants in the low resistance IMT group

Participants enrolled in the low resistance IMT group will use an identical training device, but will use a different, low intensity, training protocol (see section 5.6.4.2). In their training session which will be delivered by a trained research nurse or physiotherapist, participants will have FEV_1 and FVC readings taken with a spirometer and their MIP measured using the POWERbreathe® KH2 device before being shown how the POWERbreathe® KHP2 device works, how to remove and clean the valve and how to breathe in and out correctly using the

device. In contrast to the high resistance group, the low resistance IMT group will not be encouraged to adopt a specific breathing pattern. Instead they will be guided on how to breathe gently through the device in a manner that will minimise the risk of hypocapnia and avoid any training stimulus to the inspiratory muscles. Participants will be asked to complete the paper training diary and rate their perceived exertion (using the RPE rating scale). They will watch a modified version of the training video (with the sessions on how to increase load on the device removed) during the face-to-face meeting and will be given written instructions to take home with them.

The low resistance loading regimen (10% MIP) gives a perceptible and convincing training stimulus from the participant perspective, but this stimulus is not expected to cause a change in the physiological outcomes (change in MIP from baseline) [26]. It can be set and locked at a constant training load to prevent participants in the low resistance IMT group from manipulating it. The low resistance training regimen poses no risk to participants, but substantially improves the validity of the study for the following reasons:

i) Assuming adequate blinding, it allows the efficacy of high resistance IMT to be estimated, i.e. excluding any placebo effect of the IMT intervention;
ii) There is a theoretical possibility of contamination (participants obtaining a device and performing IMT on their own) or health behavioural change in the usual care group because of lack of blinding (although experience suggests that this is rare), therefore a comparison of IMT vs. usual care may result in a biased estimate.

We will not differentiate between high resistance IMT and low resistance IMT when describing the study to participants in the patient information materials, i.e. participants will be told they will be randomised to different types of breathing exercises either with or without a device.

5.6.4.2 Low resistance IMT training protocol

Participants in the low resistance IMT group will undertake 30 breaths, two times daily, 7 days per week, using the POWERbreathe® KHP2 at home. The training load will be set at 10% of MIP, and will remain at this level throughout. Training will continue for a minimum of two weeks and can continue until the day of surgery. Participants will also be given a usual care leaflet containing advice on deep breathing exercises.

5.6.5 Telephone support

Participants in the high and low resistance IMT groups will be given telephone helpline numbers with instructions to call the research team member who trained them to use the device at their hospital if they have any queries relating to the IMT intervention. If they have difficulties with the device itself, they will also be given the technical helpline number POWERbreathe® if they have any questions relating to the IMT intervention or are experiencing problems with the device.

5.6.6 *SMS text reminders*

Participants in the high and low resistance IMT groups who consent to receive notifications by SMS text will be sent intermittent text messages during the period of the training interventions, reminding them to perform their breathing exercises.

5.6.7 Usual care protocol

Participants will be given advice about the importance of deep breathing exercises and provided with a leaflet containing written information on peri-operative deep breathing exercises. The usual care leaflet will also be given to participants in the IMT groups.

5.6.8 Care procedures common to all three groups

For all participants, other aspects of pre-operative care (including advice about surgery) will be according to local protocols. Basic information about pre-operative care including prehabilitation programmes will be collected from participating sites.

5.7 Primary and secondary outcomes

Primary outcome

5.7.1 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. PPCs affect between 2% and 40% of patients undergoing major surgery depending on the definition used [33-35]. The variability in reporting of PPCs in the literature makes it difficult to precisely estimate the true frequency of PPCs in our patient population. We will use the composite outcome proposed by the European Society of Anaesthesiology and the European Society of Intensive Care Medicine as a consensus definition for PPC [36]. This includes respiratory failure, pulmonary infection, atelectasis, effusion, pneumothorax, aspiration pneumonitis and bronchospasm; there are specified diagnostic criteria for each component. These complications are all plausibly modified by the intervention because increased respiratory muscle strength enables patients' normal respiratory effort to exceed respiratory system compliance (typically decreased following surgery) and promote adequate pulmonary ventilation (improved gas exchange, reduced atelectasis and infection) and reduce the incidence of respiratory distress (high respiratory rate, use of accessory muscles, abnormal breathing patterns) which in turn will decrease the likelihood of respiratory failure.

This definition of PPC was used in the PERISCOPE study which reported the development of the ARISCAT tool for predicting PPCs [1]. The PERISCOPE study (prospective cohort of 5859 patients) reported a PPC frequency of 20% using this composite in a mixed surgical cohort (ARISCAT score > 26, recent personal communication) [2]. The PERISCOPE cohort included a large proportion of orthopaedic patients (20%), who are at lower risk of PPCs than patients undergoing cardiothoracic & abdominal surgery; therefore, the incidence of PPCs in our study population is likely to be higher [23].

Since funding was obtained to conduct the INSPIRE study, a new consensus definition for PPCs has been reported (Standardized Endpoints for Perioperative Medicine-Core Outcome Measures in Perioperative and Anaesthetic Care, StEP-COMPAC) [37]. However, we have kept our original definition of PPCs (see above) because this was used to estimate the event rate for the PERISCOPE cohort and was the basis for our sample size calculation.

5.7.1.2 Individual elements of the composite outcome

i) Respiratory infection
Criteria: Treatment 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/mm^3 [4, 38].

Clinical relevance: Post-operative pneumonia is common (9-40% of patients) and associated with substantial morbidity and mortality (30-46% mortality). Consequently it has face validity as a clinically important PPC.

Patient relevance: Postoperative pneumonia has patient relevance because of the associated morbidity, mortality and the association with reduced quality of life.

ii) Respiratory failure
Criteria: Postoperative PaO_2 <60 mmHg (<8kPa) on air, a ratio of PaO_2 to inspired oxygen fraction <300, or arterial oxyhaemoglobin saturation measured with pulse oximetry <90% and requiring oxygen therapy [7, 39, 40].

Clinical relevance: Respiratory failure is associated with the need for ventilation, critical care admission, and increased morbidity and mortality. It has important clinical consequences and is therefore clinically relevant.

Patient relevance: Respiratory failure is of relevance to patients as it may prolong hospital stay and increase hospital mortality and long term mortality at 5 years. Furthermore, it may result in invasive interventions such as non-invasive ventilation which may be associated with discomfort.

iii) Pleural effusion
Criteria: Chest radiograph demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm (in upright position), evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows [41].

Clinical relevance: the accumulation of fluid within one, or both, pleural cavities adversely affects the mechanics of ventilation. This impairs ventilation-perfusion matching, increases work of breathing and contributes towards the development of respiratory failure (as described above).

Patient relevance: Pleural effusion is of relevance to patients as it may prolong hospital stay, and contribute towards morbidity and mortality. It increases the risk of respiratory failure and potentially necessitates interventional procedures such as intercostal chest drain placement, which is uncomfortable and associated with the risk of complications.

iv) Atelectasis
Criteria: Suggested by lung opacification with shift of the mediastinum, hilum, or hemi-diaphragm toward the affected area, and compensatory over-inflation in the adjacent nonatelectatic lung [42].

Clinical relevance: Atelectasis commonly contributes towards the development of pneumonia and causes respiratory failure, both of which are associated with prolonged length of stay and mortality. Atelectasis is a common cause of postoperative hypoxaemia and prevention of progression to requirement for invasive mechanical ventilation has been studied in several surgical cohorts, indicating the perceived importance of this condition. Weak respiratory muscles predispose to atelectasis and therefore the benefits of inspiratory muscle training might be most sensitively appreciated through measuring rates of atelectasis.

Patient relevance: Atelectasis is commonly considered as a precursor to the development of pneumonia, commonly contributes towards respiratory failure and therefore prolongs hospital length of stay and is associated with dyspnoea, all of which are of relevance to patients.

v) Pneumothorax
Criterion: Air in the pleural space with no vascular bed surrounding the visceral pleura.

Clinical relevance: Air in the pleural space is similar to fluid in the pleural space in that it adversely affects the mechanics of ventilation - impairing ventilation-perfusion matching, increasing work of breathing and contributing towards the development of respiratory failure. In the peri-operative setting there is the additional concern about the cause of the pneumothorax, as it may represent a complication of placement of a central venous cannula, a complication of surgery (injury to the airways, lung or diaphragm), or the use of excessively high pressures during positive pressure ventilation whilst under general anaesthesia. Pneumothoraces commonly necessitate additional procedures (pleural aspiration or inter-costal drain).

Patient relevance: Pneumothoraces cause the unpleasant symptoms of breathlessness and chest pain, may require additional invasive procedures and may contribute towards the development of respiratory failure with the consequences discussed above.

vi) Bronchospasm
Criterion: Newly detected expiratory wheezing treated with bronchodilators [43].

Clinical relevance: Perioperative bronchospasm may occur in patients with a background of asthma and or COPD (approx. 1.7% of such cases). Severe bronchospasm may prolong hospital length of stay and causes respiratory failure and increased mortality (approximately 2%).

Patient relevance: Bronchospasm is associated with dyspnoea and discomfort and as such is of relevance to patients. If severe, it may result in respiratory failure with the consequences discussed above.

vii) Aspiration pneumonitis
Criterion: Respiratory failure after the inhalation of regurgitated gastric contents [44].

Clinical relevance: Failure of airway protective mechanisms rarely occurs but when it does and gastric contents pass into the lungs the effects can be fatal. It is a recognised cause of acute respiratory distress syndrome (ARDS) and accounts for up to 30% of all deaths due to general anaesthesia. In less extreme examples it can contribute towards the development of respiratory failure.

Patient relevance: Aspiration pneumonitis is associated with respiratory failure. It is of relevance to patients as it may prolong hospital stay and increase mortality risk. Furthermore, it may result in uncomfortable sensations such as dyspnoea and invasive interventions such as non-invasive ventilation which may be associated with discomfort.

Secondary outcomes

- Each of the seven individual components of the composite primary outcome (defined using
5.7.2 the European Society of Anaesthesiology and the European Society of Intensive Care Medicine [34]):
    i) Respiratory infection
    ii) Respiratory failure
    iii) Pleural effusion
    iv) Atelectasis
    v) Pneumothorax
    vi) Bronchospasm
    vii) Aspiration pneumonitis

- Postoperative ventilation;
    - Invasive ventilation;
    - Non-invasive ventilation (including continuous positive airway pressure (CPAP) and/or pressure support (BIPAP));
    - Optiflow (high flow nasal oxygen therapy);
    - For non-invasive ventilation and high flow nasal oxygen therapy we will distinguish prophylactic use from use to treat a pulmonary complication;
- Length of ICU stay;
- Length of hospital stay;
- Antibiotic prescription;
- Bronchodilator prescription;
- Patient reported outcomes (HRQoL questionnaires) (section6.3.4);
- Change in maximal inspiratory pressure (MIP) from baseline;
- Spirometry (forced expiratory volume, FEV_1 and forced vital capacity, FVC) measurements from baseline;
- Progression in training load (from baseline);
5.8 • Mortality;

- Other complications of surgery documented using the Clavien-Dindo [46] classification and the Comprehensive Classification Index [47, 48].

Sample size calculation

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%. The sample size required to achieve 80% and 90% power, assuming 5% statistical significance and a two sided test, for target differences of 8%, 5% and 3% are shown in Table 2. The primary outcome of any PPC (vs no PPC); assuming a PPC rate of 15% in the high resistance group and a PPC rate of 20% in the low resistance and usual care groups combined. 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.

Table 2 Incidence of PPCs

Incidence of PPCs		Risk ratio	Sample size (total) Power	
IMT	Low resistance IMT /usual care		90%	80%
0.12	0.20	0.6	928	708
0.15	0.20	0.75	2500	1890
0.18	0.20	0.9	16,368	12,278

By month 14 of the study (2 months before the end of the pilot phase, 6 months after the start of recruitment), we estimate that 160 participants will have been recruited to the IMT group and will have provided MIP at recruitment and before surgery. A sample of this size will allow a 0.53 SD difference in MIP between the two training strategies, to be estimated with a precision +/- 0.32 SD assuming a correlation of 0.5 between pre- and post-training measures.

6.1 6. Study methods

Description of 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).

In the SWAT (section 5.2), participants in the high resistance IMT group will be randomised in a 1:1:1:1 ratio to one of the four groups with random allocation stratified by centre and specialty.

Blinding

The study includes a low resistance IMT intervention group, set to a resistance level that is considered ineffective in influencing MIP [26]. This group has been included so that participants, their clinical care team (i.e. surgeon, anaesthetist and post-operative care team) and all
6.2 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
6.3 unblinded analyses and will not be disclosed to any other member of the research team.

6.3.1

Research procedures

Research assessments

Baseline assessments will be made before randomisation. Participants will be followed postoperatively to discharge, and at three months and six months post operatively. PPCs will be collected during hospital stay (section 5.7.1 for criteria for defining individual PPCs) using hospital notes and electronic databases. We will assess PPCs and adverse events and administer HRQoLs at three months and six months post-operatively. Follow-up for all participants at three and six months post-surgery will be by postal questionnaires, online completion using a secure login, or by telephone (participants will indicate their preferred method of follow-up). The local research team (or the co-ordinating centre, if deemed more appropriate) will contact participants at mutually agreed times.

Assessment of maximal inspiratory pressure (MIP)

Maximal inspiratory pressure (MIP) will be assessed in all study participants by a trained research nurse or physiotherapist using the POWERbreathe® KH2 device at randomisation and pre-surgery. MIP measurements will be performed from residual volume (the volume of air left in the lungs at the end of a maximal expiration). MIP assessments will be repeated at least 5 times

6.3.2 until the 3 best measurements differ from each other by less than 5 cm H_2O [21]. In Phase 1 of the study, participants randomised to receive one additional face-to-face hospital visit (section 5.2.2. Study within a trial (SWAT)) will also have MIP measured at this time point. MIP will be measured in a standardised fashion at all sites.

Assessment of spirometry

FEV_1 and FVC measurements will be assessed in all study participants using a spirometer at

6.3.3 randomisation and pre-surgery. Spirometry assessments will be repeated at least 5 times until the 3 best measurements differ from each other by less than 5cm H_2O.
Spirometry will be measured in a standardised fashion at all sites.

Assessment of patient reported outcomes

6.3.4 Generic HRQoL, using EuroQol-5D-5L questionnaire [49] and Short Form-12 (SF-12) questionnaire will be assessed at randomisation, pre-surgery, 3 months post operatively and at 6 months post-surgery. The extensively validated EQ-5D-5L will assess generic aspects of health (http://www.euroqol.org/home.html), and will be used in the analysis of quality adjusted life years (QALYs). Additionally, we will also assess the following patient reported factors at baseline and at 6 months post-surgery:

i) anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) [50];
ii) resilience using the Connor Davidson Resilience Questionnaire (CDRQ) [51];
iii) self-efficacy using the Lorig self-efficacy questionnaire [52];
iv) physical activity using the Duke Activity Status Index (DASI) [53].

Surgical regret will be assessed 6 months post-operatively using the Decision Regret Scale [54].

On admission for surgery, nutritional status will be assessed in all INSPIRE patients using the Malnutrition Universal Screening Tool (MUST) [55] and the Perioperative Nutrition Screen (PONS) [56].

Reasons for non-completion of any assessment will be recorded and coded. Missing items or

6.3.5 errors on the questionnaire will be dealt with according to the scoring manual or via imputation methods. Adherence rates will be reported in results, including the numbers of patients who have withdrawn from the study, have been lost to follow up or died. Causes of death for patients who die will be recorded by the local research teams according to their records.

Pre-operative cardiopulmonary exercise testing (CPET)

Some sites offer CPET testing [57] routinely to all patients who undergo surgery as part of perioperative assessment. We will collect the following parameters from CPET tests for all patients who participate in INSPIRE: anaerobic threshold (ml kg^{-1} min^{-1} and ml absolute); peak oxygen uptake (VO_2 peak in ml kg^{-1}, ml min^{-1} and ml absolute); ventilatory equivalent for carbon dioxide at the anaerobic threshold (VE/VCO_2 in ml kg-1, ml min-1 and ml absolute). In the

absence of an anaerobic threshold we will record the minimum VE/VCO_2 recorded during the test. These parameters assess patient fitness and the efficiency of gas exchange; we will use this information to determine whether patient fitness influences the effectiveness of IMT.

QuinteT Recruitment Intervention (QRI)

i) Stage 1: understanding recruitment issues

6.3.6 Stage 1 will focus on building up a comprehensive understanding of recruitment challenges that arise during the pilot phase of INSPIRE. A multi-faceted, flexible approach will be adopted, using the following methods:

a) Mapping patient eligibility and recruitment pathways:

Detailed eligibility and recruitment pathways will be compiled for clinical centres, noting the point at which patients receive information about the study, which members of the clinical team they meet, and the timing and frequency of appointments. Recruitment pathways will be compared with details specified in the study protocol and pathways from other centres to identify practices that are potentially more/less efficient. The qualitative researcher will also work closely with the coordinating centre, Bristol Trials Centre (BTC (CTEU)) to compose detailed logs of potential RCT participants as they proceed through screening and eligibility phases, to help identify points at which patients do not continue with recruitment to the RCT. Numbers of eligible and recruited patients will be compared across centres, and considered in relation to estimates specified in the grant application/study protocol.

b) Audio recording and observation of recruitment appointments:

Scheduled appointments during which the study is discussed will be audio-recorded and/or observed with permission, including telephone conversations. All staff involved in discussing INSPIRE with patients will be invited to audio-record (with the appropriate consent from patients) their discussions with patients using an encrypted digital recorder. The audio recordings will be used to explore information provision, recruitment techniques, management of patient treatment preferences, and randomisation decisions to identify recruitment difficulties and improve information provision. Recordings will be transferred to and from the University of Bristol (for analysis) through University of Bristol-approved secure data transfer facilities and/or encrypted flash drives that adhere to NHS Trust policies.

c) Semi-structured interviews may be conducted with:

- Members of the Trial Management Group (TMG), including the CI and those closely involved in the design, management, leadership and coordination of the study.
- Clinical and recruitment staff across all centres delivering the RCT.
- Eligible patients who are approached to take part in the RCT.

Interviews with TMG members/recruiters will investigate their perspectives on the RCT and experiences of recruitment (where relevant). Key topics explored will include views about the study design and protocol; understandings of the evidence on which the study is based; perceptions of uncertainty/equipoise in relation to the RCT arms; views about how the arms/protocol are delivered in clinical centres; methods for identifying eligible patients; views on eligibility, and examples of actual recruitment successes and difficulties.

Interviews with patients will explore views on the presentation of study information, understandings of study processes (e.g. randomisation), and reasons underlying decisions to accept or decline the study. Numbers of interviews will be guided by the concept of 'data saturation'; the need to continue sampling until findings become repetitious.

QRI interviews will take place at a mutually convenient location, in a suitably private and quiet setting. All participants will be offered the option to conduct the interview over the telephone. The University of Bristol's 'lone researcher' safety policies will be upheld for any interviews taking place in non-public settings (e.g. participants' homes).

d) Observation of TMG and investigator meetings:

It is likely that the CI, TMG and clinical investigators will meet or have telephone conferences to discuss the progress of the RCT. The qualitative researcher will observe and potentially audio-record these meetings, with permission. The aim will be to gather further information about specific issues that may have a bearing on recruitment. These meetings can also elucidate new solutions to recruitment difficulties.

e) Document analysis of study materials:

PILs, the study protocol, and other study literature will be reviewed by the trial management team to identify aspects that are unclear or potentially open to misinterpretation, thus having a possible bearing on recruitment.

ii) Stage 2: Development and implementation of recruitment strategies

Findings from Stage 1 will be presented to the CI and TMG (with permission from the CI). If recruitment difficulties are evident across the study or in particular centres, the CI/TMG and QRI team will formulate a 'plan of action' to improve recruitment and information provision. The specific plan implemented will be grounded in the findings from Phase 1, with its format dependent on the nature of the recruitment barriers identified. For instance, generic challenges such as how to explain study processes (e.g. randomisation) may be addressed through dissemination of 'tips and guidance' documents. Supportive feedback will be a core component of the plan of action, with the exact nature and timing dependent on the issues that arise. Centre-specific feedback may cover institutional barriers, while multi-centre group feedback sessions may address widespread challenges that would benefit from discussion. All group feedback sessions will be aided by anonymised data extracts from interviews and audio-recorded appointments. Individual confidential feedback will also be offered, particularly where recruiters experience specific difficulties or where there is a need to discuss potentially sensitive issues. Investigator meetings and site visits may also be employed to discuss technical or clinical challenges (e.g. discomfort surrounding eligibility criteria).

6.3.6 Iterative nature of Stages 1 and 2

The QRI has been presented as two distinct stages for clarity, although in reality these are likely to overlap or run in tandem. For instance, new avenues of enquiry may emerge through feedback meetings, which can be a route to investigating recruitment difficulties in their own right. Insights into recruitment can emerge at any point during the RCT and instigate further investigations (Stage 1) or intervention (Stage 2).

6.3.7 Audio-recording recruitment discussions

Patients will be sent a copy of the information pertaining to recording recruitment consultations for the QRI in the post. Recruiters will check if the patient has any questions about the recording process at the first recruitment appointment, and then seek written consent to record the discussion. Patients who agree will sign a one-off consent form that seeks permission to record future discussions about the study in the lead up to the patient making their decision about participation.

Where it has not been possible to send participants information in the post in advance of their appointment, they will be given the QRI information in clinic. Participants who have been given less than 24 hours to consider the study can still be consented on the condition that they are given adequate time to read and consider whether they are willing to have their appointment recorded. Participants will only be consented if they and the local research team feel they have had enough time to consider the information and ask questions that have been answered satisfactorily. If participants agree, they will sign the QRI consent form.

6.3.8 Staff interviews

Interviews with health professionals will take place throughout the study duration using purposeful sampling. Most interviews will be done via telephone, although some may be done face to face (for example to coincide with a site initiation visit, SIV). Taking part will be optional. Written informed consent will be obtained for all face to face staff interviews. The same informed consent form will be completed over the telephone for those staff not participating in face to face interviews and a note made that consent was taken over the telephone.

6.4 Duration of treatment period

The duration of the treatment commences when the participant receives face to face training on breathing exercise regimens in all three arms; high resistance IMT, low resistance IMT or usual care. The duration of the breathing exercises will be for a minimum of two weeks before the day of surgery. In some instances the surgery date may be cancelled or postponed; in such instances, the duration of treatment will be extended further until an alternative surgery date is confirmed. For non-cancer surgery (e.g. elective heart surgery), the waiting time between referral for surgery and surgery may be longer than 2 weeks; therefore, participants will be
6.5 recruited as soon as feasible and may be required to perform the intervention for up to 8 weeks before the day of surgery.

Definition of end of study

Each participant will complete a booklet containing health-related questionnaires 6 months after
6.6 randomisation. The participant's involvement in the study will end at this point. Data collection for the whole study will be complete when the final randomised participant has completed the six month post randomisation assessments. The end of the study as a whole will be after study follow up has been completed, all data queries have been resolved, the database locked and the analysis completed.

Data collection

Eligibility will be assessed after multi-disciplinary team (MDT) meetings for participants due to undergo cancer (and some non-cancer) surgery, at the outpatient clinic when a decision to operate is made, at pre-assessment clinics and by inspecting the relevant theatre lists. The following equality monitoring data will be collected for all patients including those patients who decline (to assess any differences in those that take part compared to those who do not to see if there are any socio-economic barriers to participation):

i) Age
ii) Sex
iii) Index of Multiple Deprivation (IMD) for place of residence derived from the participant's residential postcode, as recorded in the hospital patient information system;

The baseline data will be collected after consent. Each patient will be randomised after baseline data has been collected and will be assigned a unique study number. All data recorded on paper relating to the participant will be located in case report forms (CRF) folders, which will be stored securely. Staff with authorisation to make changes to the study records, including the study database, will be listed on the study delegation log maintained at each specialty/centre. Data will be collected on the numbers screened, eligible and consented, including reasons for decline. Data will be captured in a purpose designed secure database, with in-built real time validation, which will be developed by BTC (CTEU) to support the study. Resource use data will be collected using study CRFs and patient questionnaires. Data collection (see Table 3) will include the following elements:

i) A screening log of all elective patients referred for cardiac, thoracic and abdominal surgery, and those who are approached for the study (including the date when they are given the PIL);
ii) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility;
iii) Consent information collected prior to randomisation in all participating patients including reasons for non-consent;
iv) Baseline information (e.g. history and planned operation, response to health status questionnaires) collected in all participating patients;
v) Data from IMT devices recording adherence to the IMT intervention;
vi) Data recorded by patients during the IMT intervention (patient diary and RPE rating scales);
vii) Data relating to the participant's surgery, ICU stay and hospital stay (including any PPCs and any other adverse events) collected in all participating patients;
viii) Additional tests and medications (e.g. bronchodilators, antibiotics) prescribed for all participating patients during their hospital stay;
ix) Data on MIP and spirometry at the end of the intervention (when patient is admitted for surgery);
x) Data on PPCs, any other adverse events and health status questionnaires collected at 3 months and at 6 months post-surgery for all participating patients.

To minimise bias, all PPCs have been defined as far as possible on the basis of objective criteria (section 5.7.1). To minimise bias, outcome measures are defined as far as possible on the basis of objective criteria. All personnel carrying out outcome assessment (with the exception of MIP measurements) will be blinded; this will minimise detection bias.
The data collection schedule is shown in Table 3.

We will track patients for mortality for 6 months after surgery using hospital tracking systems or centrally collected data (Office for National Statistics).

Table 3 Data collection schedule

Data item	Baseline *(Pre-randomisation)*	Initial training visit* *High/low resistance IMT/usual care groups*	*Additional training visit*** *High resistance IMT group: Phase 1 only*	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.

** Additional visit for patients randomised to high intensity IMT group may coincide with POA visit.

§ Taken from patient training diary and IMT device.

Routine CPET may occur anytime between MDT & surgery; CPET data collection will be captured on or after the day of surgery timepoint

6.7

Abbreviation guide: CDRQ: Connor Davidson Resilience Questionnaire; CPET: cardiopulmonary exercise testing; DASI (Duke Activity Status Index); HADS: Hospital Anxiety and Depression Scale; IMT: inspiratory muscle training; MIP: maximal inspiratory pressure; MUST: Malnutrition Universal Screening Tool; PONS: Perioperative Nutrition Screen; POA: pre-operative assessment; PPCs: postoperative pulmonary complications.

Source data

The primary data source will be the participant's medical notes, alongside the data collection forms for the study. The completed patient questionnaires will be the primary data source for HRQoL.

Planned recruitment rate

6.8 Phase 1 recruitment will take 8 months to complete. A review of study accrual against the pre-defined progression criteria (section 5.2.6 Main study (Phase 2) will occur 6 months after recruitment commences to Phase 1 of the study. Subject to the satisfactory completion of Phase 1, Phase 2 will recruit over a 17 month period; both recruitment windows account for the staggered start to recruitment in specialities across the sites.

Numbers of eligible patients, and the percentages of these that are approached about the RCT, and consent to be randomised will be assessed throughout the study to check whether rates are being maintained or improving. It is expected that that recruitment will increase as the study teams at each centre become familiar with the study and it becomes embedded in routine clinical practice.

Participant recruitment

6.9 All potential participants will be sent or given an invitation letter and PIL (approved by an NHS Research Ethics Committee (REC)) describing the study, in advance of recruitment. The patient will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. Information about possible benefits and risks of participation will be described in the PIL. Participants will be approached for their consent and will be required to give written consent, which will only be taken if research staff feel that participants have had sufficient time to consider their participation (ideally at least 24 hours). Details of all participants approached for the study and reason(s) for non-participation (e.g. reason for being ineligible or participant refusal) will be documented. The research nurse/study coordinator/Principal Investigator (PI)/clinical research fellow will be responsible for the consent process, which will be described in detail in the Trial Manual.

6.10

Co-enrolment

6.11 Participants will not be permitted to co-enrol in the INSPIRE study if they are participating in an interventional study where the intervention is administered 3 months prior to or up to 6 months after surgery. Participants will not be permitted to co-enrol in other studies during the interventional phase of INSPIRE. Participants will be permitted to take part in non-interventional studies (e.g. observational studies) as long as the burden placed on the participant is reasonable and the other study protocol permits this (to be agreed on a study by study basis).

Discontinuation/withdrawal of participants

Each participant has the right to withdraw at any time. It is unlikely for this study that there would be any reason for the investigator to withdraw the participant from their allocated treatment, unless subsequent to randomisation, a clinical reason for not performing the surgical procedure is discovered. Information relating to a withdrawal will be recorded in all cases.

The study intervention may be stopped early if the participant experiences a serious adverse event (SAE) (see section 9.1) that the treating clinician thinks may be attributable to the study intervention or may get worse if study intervention is continued.

Participants withdrawn from their allocated intervention but willing to continue completing follow-up schedules will be encouraged to do so. All discontinuations and withdrawals will be documented. If a participant wishes to discontinue, data collected up until that point will be kept and included in the analyses.

Frequency and duration of follow up

Data for the primary outcome and most secondary outcomes will be collected during hospital stay, at 3 months and 6 months after randomisation (through postal or online questionnaires or
6.12 telephone calls).

Likely rate of loss to follow-up

6.13 Loss to follow-up for the primary and most secondary outcomes is likely to be low because data will be collected during the hospital stay or at the routine follow up appointment. Established BTC (CTEU) methods will be used to maximise the proportion of participants for whom all outcome data are available and the proportion of participants who receive the intervention to which they were allocated. After discharge from hospital, the only losses to follow-up will be due to death or participant discontinuation. We expect loss to follow-up after discharge over the 6 months of follow-up to be less than 5%, since outcome data will be collected by post, online completion and through telephone calls (i.e. the patient will not have to come in for an additional study visit).

6.14

Expenses

Participants in all three groups may require a minimum of one additional hospital visit before surgery to have their MIP recorded, and in the high and low resistance IMT groups to be given an IMT device and shown how to use it. We will try to coincide this visit with a pre-existing hospital appointment (e.g. the pre-operative assessment appointment) if this is more than two weeks before surgery.

Participants in the high resistance IMT group who are randomised in Phase 1 to one additional hospital visit to check the training load and IMT adherence may need an additional research visit which we will try to coincide with a pre-existing hospital visit if this falls between the start and end of the intervention period. Therefore, most participants will need an additional visit, a few may need two. Travel expenses will be provided for any visits made for the purpose of
7.1 research only.

7. Statistical analyses

Plan of analysis

The data will be analysed according to ITT and follow CONSORT reporting guidelines. Randomised participants who fail to complete the minimum specified duration of the intervention will be included in the primary analysis.

Analysis of the SWAT

The primary outcome will be compared using a mixed regression model, adjusted for baseline measures. The two interventions will be fitted as fixed effects and the interaction will be examined. If the interaction is not significant at the 10% level (chosen to ensure potentially important interactions are not missed), the differences in main effects will be reported, otherwise
7.1.1 the effect of loading method will be reported separately for the sub-groups with and without an extra visit.

7.1.2 Analysis of the main study

The study will allocate participants in a 1:1 ratio to IMT vs. no IMT in a 2:1:1 ratio to high resistance IMT vs low resistance IMT vs usual care. This allocation scheme has been chosen to optimise the power of the expected primary comparison, i.e. between the high resistance IMT group and the combined low resistance IMT and usual care groups. As a first stage to the analysis we will quantify the difference in primary outcome between the low resistance IMT and usual care groups. If the standardised difference in MIP is less than 0.25 SD (small effect size [58]) we will combine the low resistance IMT and usual care groups and the primary analysis of the study will compare the high resistance IMT group with the combined low IMT and usual care groups. If the standardised difference between low resistance IMT and usual care groups is greater than 0.25 SD, suggesting a placebo effect (i.e. a lower primary outcome rate with low resistance IMT than usual care), we propose the primary analysis will compare high resistance IMT and low resistance IMT, in order not to inflate the potential treatment benefit by including usual care. The study will have 75% power for this comparison. If the converse holds and the event rate is higher with low resistance IMT than with usual care by >0.25 standardised difference (unlikely), we will pool the low resistance IMT and usual care groups as above.

Analyses will be adjusted for centre, specialty and ARISCAT score. Differences in treatment effect by specialty/ARISCAT score will be assessed by adding a group x specialty/ARISCAT score interaction to the model and comparing models using a likelihood ratio test. PPCs and other binary outcomes will be compared using logistic regression. Time to event outcomes (e.g. duration of ventilation, ICU and hospital stay) will be analysed using survival methods, allowing for censoring of any participant who dies prior to hospital discharge. HRQoL and MIP will be compared using a mixed regression model, adjusted for baseline measures where appropriate. Changes in treatment effect with time will be assessed by adding a treatment x time interaction to the model and comparing models, again using a likelihood ratio test. Deaths will be accounted for by modelling HRQoL and survival jointly. Model fit will be assessed and alternative models and/or transformations (e.g. to induce normality) will be explored where appropriate. Frequencies of adverse events, including components of the primary outcome, will be described. Treatment effects will be reported with 95% CIs. 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).

A detailed analysis plan will be prepared. Interim analyses will be decided in discussion with the Data Monitoring and Safety Committee (DMSC). There is no intention to compare any outcomes between groups after the completion of Phase 1; the only analyses will be descriptive statistics to summarise eligibility and recruitment to decide whether the study satisfies the recruitment

progression criteria and a comparative analysis of the effect of intensive vs. less intensive training in the IMT group on the primary outcome.

Subgroup analyses

The following subgroup analyses are planned:

- by surgical specialty (as described in section 7.1.2);
- by ARISCAT score (26-44 vs. ≥45);

7.2

- 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 vs > 2)
- according to physical activity status at baseline (DASI score <=median vs DASI score > median [59])
- according to depression/anxiety status at baseline (HADS score <=7 vs HADS score >7) [60]

We will describe the primary and secondary outcomes in the subgroups and test for differences in outcomes between subgroups by including interaction terms in models and/or stratifying models, as appropriate.

Frequency of analyses

7.3

The primary analysis will take place when follow-up is complete for all recruited participants. Safety data will be reported to the DMSC at a frequency to be agreed, together with any additional analyses the committee requests. In these reports, the data will be presented by group (in all 3 groups) but the allocation will remain masked.

7.4

Criteria for the termination of the study

The study may also be terminated early on the instruction of the DMSC or if the results of

7.5 another study make the completion of this study unnecessary.

Qualitative data handling and analysis

All interviews will be audio-recorded, transcribed verbatim and edited to ensure anonymity of respondent. Data will be managed using NVivo software. Transcription will be undertaken by an approved transcription service/transcriber that has signed the necessary confidentiality agreements with the University of Bristol. All transcripts will be edited to ensure anonymity of respondent. Data will be managed using NVivo software and stored on encrypted drives at the University of Bristol, in line with the university's data storage policies.

Interview data will be analysed thematically using constant comparative approaches derived

7.6 from Grounded Theory methodology [61].

Audio-recorded recruitment consultations will be subjected to content, thematic, and novel analytical approaches, including targeted conversation analysis [62] and quanti-qual appointment timing (the 'Q-Qat method') [63], as described in the QRI protocol [24].

Economic evaluation

The aim of the economic evaluation is to evaluate whether IMT represents good value for money for the NHS. The within-trial cost-effectiveness analysis will be undertaken from an NHS and personal social services perspective. The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) [64], estimated using the EuroQol EQ-5D 5L [49] [65], which will be administered at baseline (pre-randomisation), pre-operatively and 3 and 6 months after surgery via post or online. A within-trial cost-utility analysis, with a time horizon from the day of randomisation until 6-months post-surgery will be conducted, as it is anticipated that most major resource use will occur within this timeframe. The economic evaluation will follow established guidelines as set out by the National Institute for Health and Care Excellence (NICE) [66]. Comparisons between groups will be made in line with the clinical analyses (section 7.1); i.e. if the standardised difference in the primary outcome between low resistance IMT and usual care is less than 0.25 SD, then our primary analysis will estimate the incremental cost and the incremental cost-effectiveness of IMT compared to no IMT (low resistance IMT or usual care).

Resource use data will be collected using the trial case report forms and patient questionnaires (at 3 months and 6 months post-surgery), and will cover length of stay in hospital (including any readmissions), time in intensive care, treating any complications, and further contact with health professionals in primary or secondary care. Unit costs will be derived from nationally published sources such as the NHS Reference Costs database (National Schedule of Reference Costs) [67] and hospital trust finances and attached to the resource use data. The costs of drugs given in hospital (including antibiotics) will be taken from the Electronic Marketing Information Tool where possible, which provides the reduced prices paid for generic drugs in hospital [68]. Drug costs not available from this source will be taken from the British National Formulary (BNF) [69].

Missing resource use and EQ-5D data will be handled using multiple imputation methods [70]. From the average costs and QALYs gained in each study group, the incremental cost-effectiveness ratio (ICER) will be derived, producing an incremental cost per QALY gained of IMT compared to no IMT. IMT will be considered cost-effective if the ICER falls below £20,000, the level below which NICE generally recommends interventions to the NHS [71]. Uncertainty around the ICER will be represented graphically on the cost-effectiveness plane by the bootstrap replicates of the mean difference in costs and QALYs between the groups. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that IMT is cost-effective for different levels of willingness to pay for health gain. This will allow decision-makers to assess cost-effectiveness at a willingness to pay threshold of their choice.

7.6.1 Sensitivity analyses

Deterministic sensitivity analyses will be used to investigate the impact on the results of the cost and cost-effectiveness analyses when varying key parameters one at a time for key cost inputs such as the IMT device and treating surgical complications, and also to investigate the impact of uncertainty on the cost-effectiveness results.

7.6.2 Economic sub-group analyses

Subgroup analyses will be conducted to investigate whether cost-effectiveness results vary between participant subgroups. The pre-specified subgroups used for the effectiveness analyses will also be used for the cost-effectiveness subgroup analyses.

8. Study management

Study oversight

Trial Management Group (TMG)

The study will be managed by a TMG which will meet face to face or by teleconference approximately every 6 weeks for the duration of the study. The TMG will be chaired by the Lead applicant and will include the CI/clinical lead and representatives from BTC (CTEU). Other members of the research team will be invited to attend as required. The TMG will be supported by BTC (CTEU), which is a UK Clinical Research Collaboration registered Clinical Trials Units. BTC (CTEU) will prepare all the study documentation and data collection forms, specify the randomisation scheme, develop and maintain the study database, check data quality as the study progresses, monitor recruitment and manage the study on a day to day basis and undertake all statistical analysis.

8.1

8.1.1

Investigator Meetings

Investigator meetings will be held approximately every 6 months to review study progress and address any issues that arise. All team members, including all study applicants, local PIs and lead research nurses will be invited to these meetings.

8.1.2

Day-to-day management

8.2

Research nurses, physiotherapists and other suitably qualified members of the local research team in each hospital (of which 1-2 members will be unblinded in order to deliver the intervention) will be responsible for identifying potential study participants, checking eligibility or gaining confirmation from a clinician when needed, obtaining written informed participant consent, randomising participants, administering training for the intervention, liaising with the theatre planning manager, collecting study data and ensuring the study protocol is adhered to.

8.3

8.3.1

Monitoring of sites

Initiation visit

Before the study commences, training session(s) will be organised by BTC (CTEU). These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

8.3.2

Site monitoring

BTC (CTEU) will carry out central monitoring and audit of compliance of centres/surgical specialties with the principles of Good Clinical Practice (GCP) and data collection procedures. The study database will have extensive in-built validation and the TMG will review the completeness and consistency of accruing data throughout the study. BTC (CTEU) will carry out a site visit and check the relevant patient medical records if following these reviews, concerns are raised by the TMG or Sponsor.

Trial Steering Committee and Data Monitoring and Safety Committee

Trial Steering Committee (TSC)

8.4 An independent TSC will be established to oversee the conduct of the study. It is anticipated that the TSC will comprise the lead investigators, an independent chair and at least two additional independent members, at least one of whom will be a patient/public representative.

8.4.1 The TSC will develop terms of reference outlining their responsibilities and operational details. The TSC will meet before recruitment begins and regularly (at intervals to be agreed with the Committee) during the course of the study.

Data Monitoring and Safety Committee (DMSC)

8.4.2 An independent DMSC will be established to review safety data during the course of the study and will advise on interim analyses. The DMSC will develop a charter outlining their responsibilities and operational details. The DMSC will meet (jointly with the TSC) before the study begins and they will meet regularly thereafter (at intervals to be agreed with the Committee). Stopping rules for the study will be discussed at the first DMSC meeting, and decisions documented in the DMSC Charter.

9. Safety reporting

9.1 Definitions

An adverse event (AE) is any undesirable event in a subject receiving treatment according to the protocol, including occurrences which are not necessarily caused by or related to administration of the research procedures.

An adverse reaction (AR) is any undesirable experience that has happened to a subject while taking a drug that is suspected to be caused by the drug or drugs.

A serious adverse event (SAE) is any event which results in death, is life threatening, requires hospitalisation or prolongs hospitalisation, results in persistent or significant disability or incapacity.

A suspected serious adverse reaction (SSAR) is any serious adverse event that is suspected to be related to the drug or drugs being taken.

9.2 Suspected unexpected serious adverse reaction (SUSAR) is an untoward medical occurrence suspected to be related to the drug or drugs being taken that is not consistent with the applicable product information and is serious.

Overview

Serious and other adverse events (AEs) will be recorded and reported in accordance with GCP guidelines and BTC (CTEU)'s Serious Adverse Events and Safety Reporting Standard Operating Procedure (SOP-GE-012) (see Figure 2).

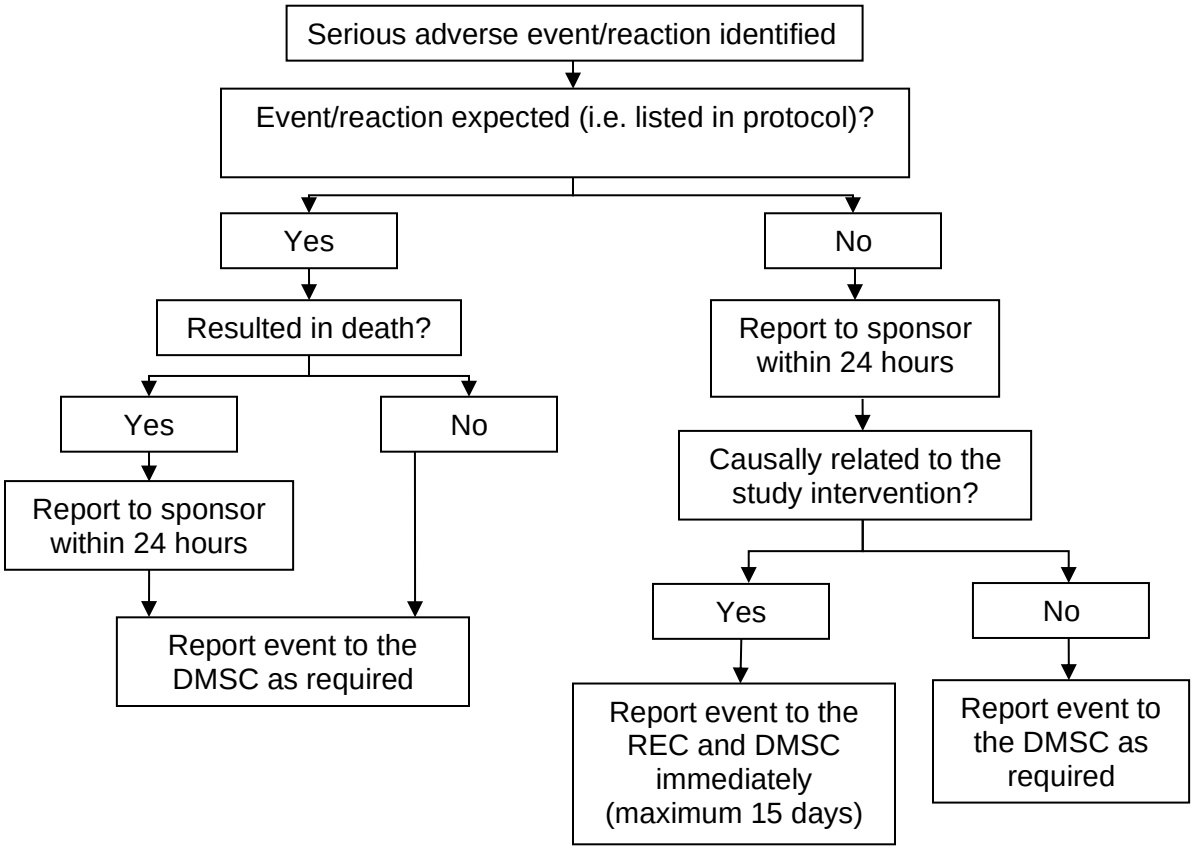
As there are no known long term safety concerns associated with using IMT, and any adverse events associated with IMT can only occur whilst the participant is undertaking IMT, safety reporting to the Sponsor will take place only while the participant is exposed to the intervention. In practice this means that the SAE reporting period will commence at the training session and continue until the patient is admitted to hospital for their index procedure. SAEs may be identified by ad hoc reporting from the patient, data collection at the extra training visits (where applicable) or on admission to hospital.

The complications or side effects of IMT, i.e. 'expected events' may include: dyspnoea, headache, pain, cough, nausea, chest discomfort, tachycardia, bradycardia, syncope, hypertension, bronchospasm, dizziness, syncope, epistaxis, respiratory distress, respiratory failure, perforated eardrum, cephalalgia. Any other event will be considered 'unexpected'. It is worth noting that the 'expected events' are events considered in other RCTs of IMT, but none of the RCTs have reported differences in the rate of any of these events between IMT/non-IMT groups, therefore these events may be regarded as hypothetical.

All unexpected and fatal SAEs will be reported to the coordinating centre, who will check the report and then forward to the Sponsor. Reporting to the Sponsor will occur within 24 hours of the site team becoming aware of the event. If the event is ongoing at the time of initial reporting the participant will be actively followed up and a follow-up report will be provided within 5 days of the initial report. Further follow up reports will be submitted only when there has been a significant change/update of the SAE until the SAE has resolved, or a decision for no further follow-up has been taken by the local PI.

All AEs during the participant's hospital stay and SAEs after hospital discharge will be recorded in detail on a CRF. At the conclusion of the study, all AEs recorded during the study will be subject to statistical analysis, and the analysis and subsequent conclusions will be included in the final study report.

Figure 2 Serious adverse event reporting flow chart



9.3

Period for recording serious adverse events

Data on SAEs will be collected for each participant from the start of their training session until the end of their 6 month follow-up period or withdrawal from the study. SAE reporting to the Sponsor will only occur during the period when participants are exposed to the intervention.

10.1

10. Ethical considerations

Review by an NHS Research Ethics Committee

The study will comply with the Declaration of Helsinki (http://www.wma.net/) on research involving human subjects. The study protocol, PIL and consent form and any subsequent amendments to these documents, will be submitted to the Sponsor, Health Research Authority (HRA), and an NHS REC for approval. All participating sites will need to confirm capability and capacity to deliver the protocol. The study will be conducted in accordance with the GCP guidelines, UK Data Protection Act 2018 and the UK Policy Framework for Health and Social Care Research. Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC and / or HRA for approval prior to implementation.

Patient and Public Involvement (PPI)

The patient, carer and public involvement and engagement (PCPIE) support group from the Royal College of Anaesthetists reviewed the proposal and will provide ongoing support. We will continue to use this group as well as the cardiac surgery PPI group established at the Bristol Cardiovascular National Institute for Health Research (NIHR) Biomedical Research Unit (BRC)

10.2 and the perioperative medicine PPI group established at the University Hospital Southampton NIHR BRC. Patient and Public Involvement (PPI) input is crucial to the success of the study and will provide invaluable input (particularly during Phase 1) which will feed into how patients will be approached and recruited to the study, and how the information about the different interventions will be presented to them.

Risks and anticipated benefits

10.3 IMT is a safe intervention; all RCTs assessing the safety and efficacy of IMT in surgical populations that reported the incidence of adverse events caused by IMT, reported that there were no adverse events [12].

The main benefit to participants is the anticipated reduction in PPCs and the potential for quicker recovery after surgery. The main potential benefit to society is improved patient experience of surgery and post-operative recovery, which can lead to quicker discharge from hospital and therefore improve efficiency and flow through the healthcare system.

11. Research governance

This study will be conducted in accordance with:

- Good Clinical Practice (GCP) guidelines
- UK Policy Framework for Health and Social Care

11.1

Sponsor approval

The study protocol and other study documents will be submitted to the Sponsor for sponsor assessment prior to submission to the regulatory authorities. Any changes to the protocol will be

11.2 reviewed by the funder. The TSC and funder will also be invited to review and approve any other amendments to the study documents prior to submission to the HRA/REC or other regulatory authorities.

NHS approval

Confirmation of capability and capacity from the local NHS Trust is required prior to the start of the study at each site.

Any amendments to the study documents approved by the HRA/REC will be submitted to participating sites for either (i) review of ongoing capacity and capability or (ii) notification only.

Investigators' responsibilities

Investigators will be required to ensure that local research processes have been followed and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study
11.3 documentation or source data on request for monitoring visits and audits performed by the Sponsor or BTC (CTEU) or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved by the HRA/REC that they receive and ensure that the changes are complied with.

Monitoring by sponsor

11.4 The study will be monitored in accordance with University Hospitals Bristol's Monitoring and Oversight of research activity SOP 010. All study related documents will be made available on request for monitoring and audit by UH Bristol, the relevant Research Ethics Committee and for any other regulatory authorities.

Indemnity

11.5

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference no. 2 refers. If there is negligent harm during the clinical study when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the study. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

12.1 12. Data protection and participant confidentiality

Data protection

12.2 Data will be collected and retained in accordance with the UK Data Protection Act 2018 and General Data Protection Regulation (GDPR) 2016.

12.2.1

Data handling, storage and sharing

Data handling

Data will be entered into a purpose-designed database hosted on the NHS network. Information capable of identifying participants will only be accessible to the individuals administering the interventions at the participating site, and to the study statistician at the co-ordinating centre. Information capable of identifying participants will not be made available in any form to those outside the study.

Access to the database will be via a secure password-protected web-interface. Study data transferred electronically to the University of Bristol network for statistical analyses will be pseudo-anonymised and transferred via a secure network. The participants will be identified using their name and unique study identifier on the secure NHS hosted database.

Data will be entered promptly and data validation and cleaning will be carried out throughout the study. The study manual will cover database use, data validation and data cleaning. The manual will be available and regularly maintained.

Data storage

12.2.2 All study documentation will be retained in a secure location during the conduct of the study and 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. If medical records are paper based and study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study (this does not apply to electronic patient notes). In compliance with the MRC Policy on Data Sharing, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University of Bristol server).

Data sharing

12.2.3 Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review.

13. Dissemination of findings

A full report will be written for the Health Technology Association (HTA) and the findings will be presented at national and international conferences, and the results published in peer-reviewed journals. Several aspects of the study (e.g. the inclusion of both a low resistance IMT and usual care arms will allow us to assess the efficacy of blinding such an intervention) will inform RCTs of lifestyle interventions in general and these will be reported at methodology meetings. We will also link with the British Heart Foundation, Cancer Research UK, the Royal College of Anaesthetists and the James Lind Alliance Priority Setting Partnership for Anaesthesia and Perioperative Care, the UK Perioperative Medicine Clinical Trials Network, the National Institute of Academic Anaesthesia (NIAA) and NIAA Health Services Research Centre, the European Society of Anaesthesiology, and other relevant clinical studies groups (CSGs) (e.g. lung cancer CSG). We will use social networking media to disseminate and publicise the study via a website or social media streams. We will also work with our PPI groups to identify how we can best publicise our findings.

Expected outputs include publication of the results of the RCT informing clinicians and patients on the efficacy of IMT for preventing postoperative complications. The study will also provide information on the feasibility of delivering a lifestyle intervention in a pragmatic fashion to

patients in the NHS setting. The health economic evaluation will provide evidence on the cost effectiveness of IMT and whether it presents value for money for the NHS. The results of the study will inform national and international guidelines on optimising the perioperative care pathway.

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15. Amendments to protocol

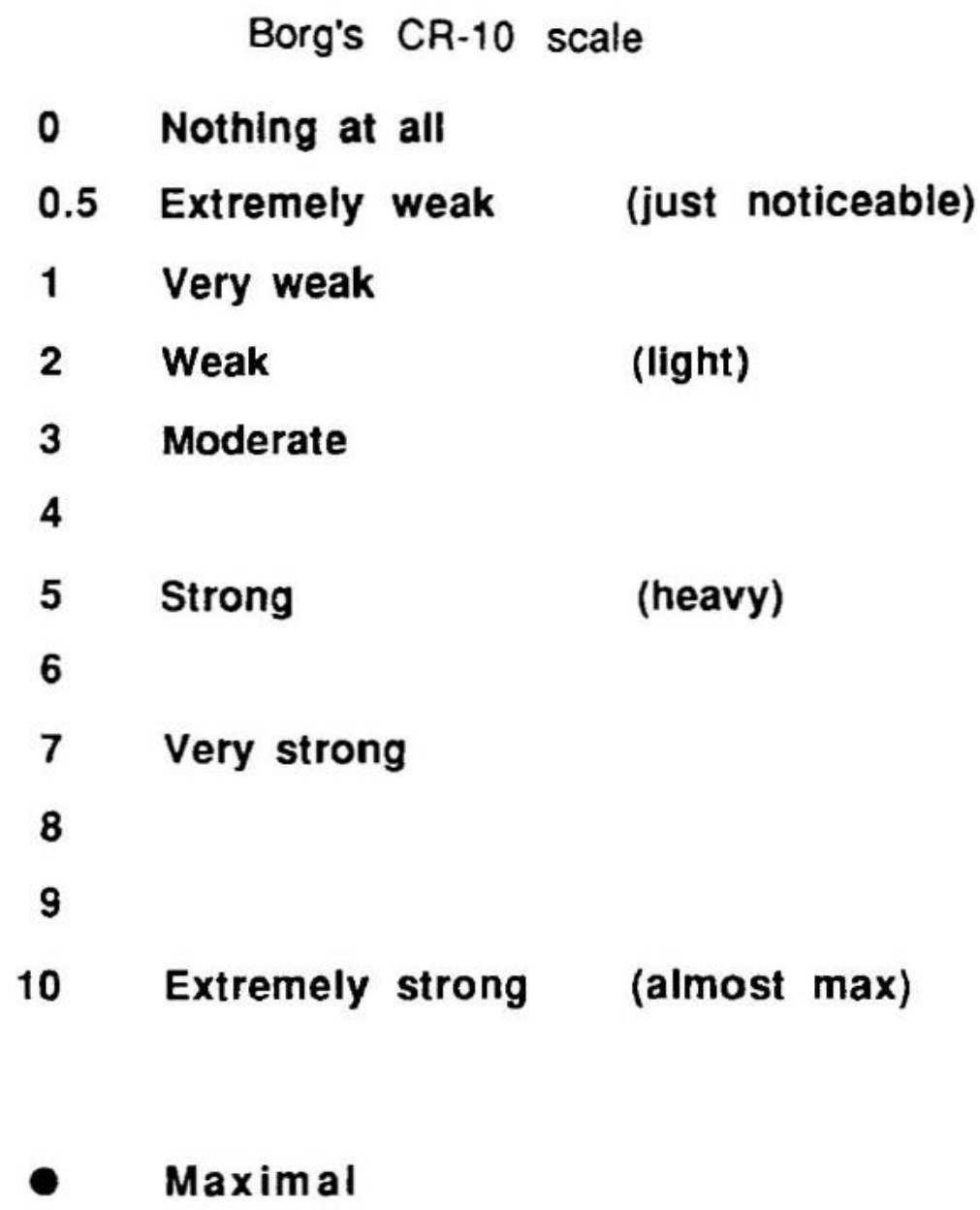
Amendment number (i.e. REC and/or MHRA amendment number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
Substantial amendment 2	V1.0	05.03.2019	V2.0	14.02.2020	- Department change of name from CTEU Bristol to BTC (CTEU). - Section 5.6.3.2 High resistance IMT protocol: wording modified to explain that patients can complete 'at least 20 breaths' instead of 30 breaths. - Section 5.7.1 Primary outcome: Removal of StEP-COMPAC definitions of post-operative pulmonary complications. Definitions from the PERISCOPE study will continue to be used. (Study schema in section 5.1	

					also updated to reflect change). - Section 5.7.2 Secondary outcomes: StEP-COMPAC definitions removed from the list. - Section 6.3.3 Assessment of spirometry: Spirometry will not be performed at the additional visit for those randomised to an additional visit (original inclusion was an error). - Section 6.5 Definition of end of study: Reference to patients completing 3 questionnaires incorrect; re-worded to explain that patients will receive a booklet containing health-related questionnaires. - Section 6.6 Data collection: We will collect age, sex, and Index of	

					Multiple Deprivation (IMD) for all participants added, - Section 9 Safety reporting: SAEs will only be reported to the Sponsor whilst the patient is undertaking IMT (the intervention). A small number of expected adverse events can be associated with IMT and have been added. SAE reporting will not take place after the index operation; list of anticipated events removed. SAEs will still be collected during the hospital admission and during the follow-up period.	

16. Appendix

Figure 2 Borg scale



[30]

Figure 3 5% work load 'look up' table

Current load	New Load	Current load	New load	Current load	New load	Current load	New load
10	11	33	35	56	59	79	83
11	12	34	36	57	60	80	84
12	13	35	37	58	61	81	85
13	14	36	38	59	62	82	86
14	15	37	39	60	63	83	87
15	16	38	40	61	64	84	88
16	17	39	41	62	65	85	89
17	18	40	42	63	66	86	90
18	19	41	43	64	67	87	91
19	20	42	44	65	68	88	92
20	21	43	45	66	69	89	93
21	22	44	46	67	70	90	95
22	23	45	47	68	71	91	96
23	24	46	48	69	72	92	97
24	25	47	49	70	74	93	98
25	26	48	50	71	75	94	99
26	27	49	51	72	76	95	100
27	28	50	53	73	77	96	101
28	29	51	54	74	78	97	102
29	30	52	55	75	79	98	103
30	32	53	56	76	80	99	104
31	33	54	57	77	81	100	105
32	34	55	58	78	82	101	106