Implementation of a Trimodal Prehabilitation Program as a Preoperative Optimization Strategy in Cardiac Surgery and Heart Transplant

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STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN.

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Subproject: #1

A single-center, ambispective cohort study is designed involving consecutive elective heart transplantation candidates from July 2017 to July 2021 once officially included in the waiting list. The trial has obtained local ethical committee approval (HCB/2017/0708). Written consent will be obtained for all patients participating in the prehabilitation group.

- *Participants*

From July 2017, all patients included in the waiting list for elective heart transplantation will be considered for inclusion in the prehabilitation program. Exclusion criteria are clinical instability precluding exercise training, refusal, or unavailability to participate. Exercise training sessions will be delivered at the outpatient clinic and patients' agreement to attend twice weekly for at least eight weeks (intensive phase) is considered a mandatory requirement.

The control group will be consisted of a historical cohort of consecutive elective heart transplantation recipients from 2014 to 2017 (prior to the implementation of the prehabilitation program on July 2017), and contemporaneous elective heart transplantation recipients who will not be involved in the prehabilitation program due to logistic issues (waiting-list period <2 weeks or not being able to attend twice a week). Data from those patients will be obtained from the transplant database and hospital medical records.

- *Intervention*

A baseline assessment of prehabilitation patients will be performed during the first week after being included in the heart transplantation waiting list and all participants will be reassessed eight weeks thereafter, once the intensive training phase is completed.

The assessment consists of (i) clinical history and physical examination; (ii) Clinical Frailty Scale (CFS); (iii) forced spirometry test (BodyBox Plethysmography; Medisoft; Sorinnes, Belgium); (iv) functional capacity evaluation by standard incremental cycle ergometer cardiopulmonary exercise testing (CPET) and endurance time (ET) measured by a cycling constant work-rate exercise testing at 80% of peak oxygen uptake (Ergocard Professional; Medisoft; Sorinnes, Belgium), 6-Minute Walking Test (6MWT), hand-grip strength, and 30" Sit-To-Stand (STS) test; (v) physical activity by the Yale Physical Activity Survey (YPAS); (vi) health-related quality of life by Minnesota Living with Heart Failure Questionnaire (MLHFQ); (vii) emotional status by Hospital Anxiety and Depression Scale (HADS); and (viii) nutritional status by Patient-Generated Subjective Global Assessment, a 3-day food record, and nutritional profile determined by blood sample analysis.

- *Prehabilitation Program*

The intervention is designed to improve (i) functional capacity by exercise training and promotion of physical activity, (ii) nutritional status by nutritional counseling and whey protein supplementation, and (iii) psychological resilience using mindfulness therapy.

The physical program includes three main actions: (i) a motivational interview, (ii) a moderate to high-intensity exercise training program, and (iii) promotion of daily physical activity. The exercise training will consist of one-hour sessions of individualized, supervised moderate to high-intensity interval training (HIIT) and resistance training at the hospital outpatient gym facility twice weekly for eight weeks. A sports cardiologist will perform the exercise training prescription, and the sessions will be conducted by a physical therapist.

HIIT will be performed on a stationary bicycle (Bike Forma; Technogym; Cesena, Italy). The program is personalized to subjects according to their peak work rate (WR) performed on CPET at baseline assessment. Each session will include 5 min of warm-up and 5 min of cool-down pedaling at 30–40% of the peak WR. The interval training will consist of at least five rounds combining 2 min of high-intensity exercise (starting at 70% of peak WR and progressing to 90–100% of peak WR through the program) interspersed with 3 min of low-intensity recovery periods (40–50% of the peak WR). WR progress during the sessions will be tailored on an individual basis, according to the subjects' symptoms and response to the exercise in previous sessions, to maximize the training effect. All subjects will be monitored during the HIIT using a 3-lead electrocardiogram, pulseoximetry, non-invasive arterial pressure, and levels of self-perceived exertion using the modified Borg scale. Strength training will be performed (if not contraindicated) and consists of upper-limb and core muscle exercise based on local muscular exhaustion within the range of 6 to 12 repetitions and avoiding Valsalva maneuvers. The intensity and/or the number of repetitions will increase every week when symptomatology allows it. In addition, all patients will be instructed on breathing exercises with an incentive inspirometer (Coach 2; Smith Medical; London, UK).

After completing the first eight weeks and until heart transplantation, patients will follow a mixed maintenance program consisting of one session per week of supervised exercise training and were encouraged to maintain a physical activity plan using community-based facilities or home-based exercising.

The nutritional intervention includes nutritional education and a tailored dietary plan according to clinical nutrition in surgery ESPEN guidelines based on the Mediterranean diet. Moreover, participants will be prescribed dietetic recommendations to enhance protein intake including whey protein supplementation (Fresubin® protein powder, Fresenius- Kabi, Madrid, Spain) within 1 h after exercise to maximize muscle protein synthesis, and before going to sleep to achieve an intake of 1.5–2 g/kg/day of protein. These recommendations will be prescribed to all patients if not contraindicated and individualized advice will be given if any other supplementation is needed.

All patients will be invited to attend a weekly mindfulness group session. This anxiety-coping intervention is strongly recommended to those patients showing signs of

anxiety/depression (defined by a HADS score >8). A weekly 60-min group session of breathing and relaxation exercises will be conducted by a mindfulness-based stress reduction expert psychologist.

Usual care for both groups consists of regular cardiological follow-up with medical and heart failure nurse visits, physical activity recommendations, intravenous iron administration if iron deficiency anemia, and nutritional intervention if needed.

- *Costs*

The analysis will include heart transplantation surgical procedures, direct hospitalization (until discharge), and prehabilitation costs. Data will be obtained through microcosting techniques according to resource use, combined with diagnostic-related center-specific hospital fees. Prehabilitation costs include specialists' fees (physical therapist, nutritionist, and psychologist), gym structural costs (hospital-specific fee), and protein costs.

- *Outcomes*

Predefined main study outcome variables assessment will be blinded to the interventional groups and included: in-hospital complications according to Clavien-Dindo Classification and Comprehensive Complication Index (CCI), postoperative mechanical ventilation time, intensive care unit (ICU) length-of-stay and total hospitalization stay, destination at hospital discharge (home vs. rehabilitation facility), and hospital readmissions during the first 30 days as well as mortality at 30 days, 3 months, and 1 year. To minimize variability, it is important to note that decisions about ventilation time, ICU length of stay, and total length of stay as well as the discharge from ICU to a normal ward, and the destination at hospital discharge will follow standardized procedures according to the center protocol.

- *Statistical Analysis and Sample Size Estimation*

Study data will be exhaustively collected and managed using Research Electronic Data Capture (REDCap) tools.

Considering CCI as the primary outcome and assuming a pooled standard deviation of 20 units, the study would require at least a sample size of 28 for each group to achieve a power of 80% and a level of significance of 5% (two-sided), for detecting a true difference in means between the test and the reference group of −15 (from 50 to 35) units.

Continuous variables will be described by mean (standard deviation) or median (interquartile range (Q1–Q3)) as appropriate, while categorical variables will be presented as frequencies (percentages). Costs will be described by median (interquartile range (IQR)), and the difference between control and intervention (prehabilitation) groups, so positive values should be interpreted as savings.

The normality of distribution will be assessed with the Shapiro-Wilk Test. Between-group comparison of continuous variables and costs will be performed using either Student's *t*- test or the Mann–Whitney U test according to their distribution while Pearson's χ^2 test or Fischer's test will be used for categorical variables. Quantile regression will be used for medians. To control for the usually skewed distribution of costs, a bootstrapping analysis will be performed to increase the robustness of the analysis.

All comparisons will be two-sided, with a significance level of 0.05. All statistical analyses will be made with R version 4.0.2, (R-Foundation, Vienna, Austria) software or STATA v.17 software.

Subproject: #2

This is a prospective, randomised, open-label, controlled trial with allocation ratio 1:1 comparing standard of care versus 4–6 weeks of a multimodal prehabilitation programme. The recruitment period is scheduled from March 2018 to January 2021. Both primary endpoint and baseline data will be blindly assessed. Intention-to-treat criteria will be used in order to define the analysis population; all randomised patients will be included in the analysis according to assigned group. The study protocol and informed consent have been evaluated and accepted by the Medical Research Ethics Committee at Hospital Clinic de Barcelona (2017/0708). The trial will be conducted according to the rules of Good Clinical Practice.

METHODS AND ANALYSIS

- Setting

This trial will be conducted in a single academic tertiary hospital in Barcelona, Spain (Hospital Clinic de Barcelona). Assessments and study interventions will be performed at the outpatient ambulatory infrastructure of Hospital Clinic de Barcelona. Surgery and postoperative hospitalization will take place in the aforementioned hospital.

-Eligibility criteria

Inclusion criteria: Patients older than 18 years old scheduled for CABG and/ or valve surgery, with an expected waiting time before surgery of 6 weeks or more and that accept to participate in this clinical trial.

Exclusion criteria: Functional or anatomical physical impairment that makes it impossible to complete the assessments and the prehabilitation programme, determined by an experienced physiotherapist in cardiopulmonary rehabilitation; cognitive impairment that would impede understanding of study procedures, informed consent or study questionnaires; cardiac instability; dynamic left ventricle outflow tract obstruction, proven exercise induced arrhythmias; other comorbidities that imply clinical instability; patient refusal to participate in the study or impossibility to attend

supervised training sessions. Specifically, we will not exclude patients with severe pulmonary hypertension or severe valvular stenosis.

-Study outline

Participant screening, recruitment, randomization and informed consent (T-1)
Participant selection will begin after surgery is proposed by the cardiac surgeon and a referral for preoperative evaluation is done. Within 1 week of the referral patient will be seen by an anaesthesiologist who will screen for eligibility criteria and will explore the willing of participating in a study related with cardiopulmonary reserve and postoperative outcome. If eligibility criteria are met, patient will be approached by a research medical staff involved in the trial. The research medical staff in charge of obtaining informed consent will randomize prior to meeting with the patient and proposing study participation.

Participants will be randomised with 1:1 ratio by a computer-generated sequence using Macro-SCReN soft- ware V.4.8.1.8302 (2018 Elsevier).

Baseline assessment (T0)

After signing the informed consent all participants will undergo a full blinded baseline medical, functional, nutritional and psychological assessment. Allocation to study group will be revealed to the part of the research team that will carry out the intervention once baseline assessment is completed. The functional capacity assessment will be conducted by a physiotherapist on different days to avoid fatigue related to it, and will consist in a standard incremental cardiopulmonary exercise testing on cycloergometer (CPET), where physiological variables in response to exercise and workload in watts (W) will be measured at the anaerobic threshold and at VO_2 peak, Endurance time (ET) in seconds will be measured by a cycling constant work-rate exercise test performed at a load equivalent of 80% of the peak workload (PWR) the patient could tolerate on the incremental CPET (Ergo- line 900, Ergoline, Bitz, Germany and Ergocard Professional, Medisoft, Sorinnes, Belgium). It will detect the responsiveness of interventions in terms of improved exercise capacity. Participants will also undergo hand grip strength test (Jamar Hydraulic Hand Dynamometer; Sammons Preston, Bolingbrook, Illinois, USA), 6min walk test (6MWT) and sit-to-stand (STS) test. The 6MWT will assess functional capacity in relation to activities of daily living. Constant work rate exercise test and 6MWT are complementary in the comprehensive evaluation of these patients. Nutritional status will be assessed by a registered dietitian using the Patient Generated Subjective Global Assessment, weight, body mass index, prealbumin and glycosylated hemoglobin (HbA1c). American Society of Anesthesiologists status, Charlson Comorbidity Index and Euroscore II data will be recorded. Physical activity will be measured by the Yale Physical Activity Survey (YPAS), functional capacity by Dukes Activity Status Index questionnaire and Anxiety and depression measured using the Hospital and Anxiety Scale (HADS). All patients will be reassessed using the same tests before undergoing cardiac surgery (T7) and at 3 months postoperatively (T9).

-Procedures

Standard of care (T1–T6): Participants in the control group will follow the standard preoperative protocol at Hospital Clinic de Barcelona that includes physical activity recommendation, nutri- tional and smoking cessation advice. Moreover, patients suffering from iron-deficiency anaemia will receive intra- venous iron infusion.

Multimodal Prehabilitation programme (PreHab) (T1–T6): Participants in the intervention group will undergo, in addition to the standard of care aforementioned, a 4–6week personalized multimodal prehabilitation programme. The interventions included will be patient-centred aiming to optimize patients' preoperative health status while enhancing their empowerment and engagement. The main components of the programme will consist in:

1. Supervised exercise training programme: 1-hour session, two sessions per week at the hospital outpatient gym facility conducted by a physiotherapist. Heart rate, blood pressure, oxygen saturation and perceived exertion rate using the modified Borg scale will be monitored throughout the training session.

i. Endurance training will be performed on stationary bicycle (Bike Forma; Technogym; Cesena, Italy) and will be tailored to the participants ac- cording to their PWR (baseline CPET). Each session includes 5min of warm-up and 5min of cool-down pedalling at 30%–40% of their PWR. An interval training consists in at least 5 bouts combining 2 min of moderate to high-intensity exercise (starting at 70% of PWR and progressing to 90%–100% of PWR throughout the programme) interspersed with 3min recovery periods at lower intensity (40%–50% of the PWR). Progression during the sessions will be tailored on individual basis to maximize the training effect.

ii. Strength training will consist in 2–3 upper (pectorals and latissimus dorsi) and lower (quadriceps) limb exercises based on 2–3 sets of 8–12 repetitions avoiding valsalva's manoeuvres. The training is performed in a modular training station using external load (Plurima Multistation Wall, Technogym; Cesena, Italy). At the first session, the physiotherapist obtains for each muscle group, the tolerated weight for the eight-repetition maximum test, to establish the initial weight for the strength training. The weight and/or the number of repetitions will increase every week to ensure strength progression and maximize the training effect. The strength training is performed 2 days per week (in combination with the endurance training).

2. Promotion of physical activity and healthy lifestyle: a physiotherapist adequately trained in behavioural strategies will use motivational interviewing techniques to promote physical activity and healthy lifestyle. The motivational interview will focus on empathy, reflective listening and affirmation, and will address the patients' barriers and limitations related to physical activity, to get a change in behaviour.
3. Respiratory physiotherapy: patients will be instructed on daily breathing exercises (chest expansions, diaphragmatic respirations and deep inspirations) with a volumetric incentive spirometer (Coach 2; Smith Medical; London, UK), at least twice per day, 1–2 sets of 10–15 breathings for each exercise.

4. Nutrition counselling and supplementation: participants will meet with a registered dietitian that will assess their nutritional status and their diet based on a self-reported 3-day food diary. Nutritional teaching and a Mediterranean, well-balanced cardioprotective diet will be instructed. An adequate protein intake of 1.2–1.5 g/kg/day will be aimed to meet the European Society for Clinical Nutrition and Metabolism recommendations. If patient does not reach the recommended daily protein intake with diet, protein supplementation with whey protein (Fresubin Protein powder, Fresenius Kabi España) will be provided to reach the aforementioned daily protein intake.
5. Weekly mindfulness sessions: Patients will be invited to attend 1 weekly hourly session of Mindfulness-Based Stress Reduction conducted by a registered psychologist. It will be strongly recommended to those who reported high rates of anxiety and depression on the baseline HADS.

Compliance to the prehabilitation programme will be calculated counting the number of supervised sessions attended out of the total intended sessions. The occurrence of any exercise-related adverse events during the prehabilitation period will be recorded and will be reported immediately to the principal investigator.

Preoperative (T7) and 3-month postoperative functional assessment (T9): All participants' functional capacity will be reassessed before surgery and 3 months postoperative using ET, hand grip strength test, 6MWT and STS test. Anxiety and depression and physical activity questionnaires will be also recorded at these time points.

Surgery and hospital admission (T8): Surgery will take place in the habitual waiting timeframe and will be performed by the regular cardiac surgery teams present in Hospital Clinic de Barcelona. Perioperative clinical protocols will be followed in a usual fashion independently of the group allocation or study participation. Hospital staff, anesthesiologists, surgeons, nurses and other people involved in patient care will be blinded to the study arm. Intraoperative complications or events as well as the need blood product transfusion or any deviation from normal course will be recorded in the intraoperative case report form (CRF).

The primary outcome of this study is the incidence of postoperative complications before patient discharge from the hospital. The type of complications included will be classified following the standards of the European Society of Anesthesiology and the European Society of Intensive Care medicine: Acute kidney injury, acute respiratory distress syndrome, arrhythmia, cardiac arrest, cardiogenic pulmonary oedema, deep vein thrombosis, delirium, gastrointestinal bleed, infection, source uncertain, laboratory confirmed bloodstream infection, myocardial infarction, pneumonia, paralytic ileus, post- operative haemorrhage, pulmonary embolism, stroke, surgical site infection and urinary tract infection.

The severity of complications will be also recorded, as a secondary outcome measure, following the Clavien- Dindo classification. To ensure accuracy of the primary endpoint, the data will be collected by a physician member of the team, every day according to standard clinical care, and then reviewed by another researcher. Both of them will be

blinded to the study group to avoid bias. Patient- chargeable costs (ie, pharmacy and blood bank); tariff- chargeable costs (ie, medical care, diagnostic techniques, laboratories, interconsultations); other healthcare resources use (ie, ICU stay, total hospitalisation length of stay, readmissions, emergency room visits) and survival will be also assessed at 3 months and 1 year postcardiac surgery by chart review.

Data collection management and monitoring: All participant's de-identified data collected at different time points will be entered by research staff members into Research Electronic Data Capture (REDCap) CRF via a secure webpage interface. Online data will be stored in a safe server located the Hospital

Data monitoring: Previous experiences in prehabilitation studies show a clear absence of safety problems related to the experimental procedure. In addition, it is an unmasked trial, which is easier and faster to detect a problem and take appropriate measures.

The investigators of the present study are responsible for ensuring that the study meets the proposed milestones and deadlines. They will also be responsible for all aspects of the study design, management, ethical conduct, analysis and dissemination of results.

Safety data, including new hospitalisation, worsening angina or heart failure and arrhythmias, will be captured and all adverse events will be reported. They are responsible to periodically evaluate the study data for participant safety and study conduct, in addition to making modifications and/or termination of the trial after communication to the Ethics Committee of Clinical investigation of Hospital Clinic de Barcelona.

- *Outcomes*

Clinical outcomes

The primary outcome variable of the study is the incidence of postoperative complications classified following the standards of the European Society of Anaesthesiology and European Society of intensive Care Medicine.

Secondary outcome variables will be: (1) severity of postoperative complications using Dindo-Clavien classification; (2) hospital and ICU days of stay and (3) 3-month and 1-year mortality. Other outcome variables include: (1) ET measured by a cycling constant work-rate exercise testing at 80% of peak oxygen uptake; (2) distance covered in the 6MWT; (3) STS test and hand-grip strength; (4) physical activity by the YPAS and (5) hospitalisation direct costs and use of healthcare resources into the follow-up 1-year period after surgery.

Outcomes for feasibility of prehabilitation include incidence of adverse events during training, compliance to the supervised training sessions and adherence to the programme.

- *Statistical analyses*

Sample size for this trial has been calculated based on the primary outcome of the study that is the reduction of incidence of postoperative complications in the prehabilitation group. Our own data in a similar population of patients indicated that the incidence of postoperative complications was 30%. Accepting a two-sided alpha-risk of 0.05 and beta-risk of 0.20, anticipating 10% of drop- outs, indicated the need of including 80 participants per group to detect a reduction of the percentage of patients with complications in the intervention group compared with the control group 20%. No adjustment for multiplicity was proposed due to this is a clinical trial with one primary outcome and without needed of interim analyses.

This trial will use intention-to-treat criteria for main analysis; nevertheless, analysis per protocol will also be performed as supportive analysis. Categorical variables, as well primary outcome, will be analysed with Fisher's exact test. Continuous variables will be compared with Student's t-test for independent groups and Mann-Whitney U test according to each variable distribution. Ordinal variables will be analysed by Mann-Whitney U test.

Secondary outcomes looking at the difference between groups for the change in functional capacity over the different time points (repeated measures) will be analysed using generalized estimating equations models and will be shown as estimated effect and their 95%CI. For these analyses, we will apply unstructured matrix in order to assess intra-subject correlation, for cases with no adjustments we will apply an autoregressive model (AR) (1) type matrix.

A cost-effectiveness study will be carried out from the perspective of the hospital, taking into account the costs of the intervention and the expenses related to the disease during the follow-up (30 days). For costs, the mean or median and their 95%CI of difference in per-patient costs between the two groups will be computed (control-group costs minus prehabilitation-group costs), so that positive values will be interpreted as savings of the prehabilitation programme. Considering previous experience with prehabilitation cost analysis, a highly skewed distribution will probably be present. Right-sided asymmetric distribution appears when some patients incur in high costs, mainly because of major medical complications. To deal with this, a non-parametric approach (bootstrapping) will be used. Bootstrap analysis yields more robust when dealing with skewed cost data compared with non-parametric tests.

- Perioperative neurocognitive disorders subproject

Inclusion criteria: Patients included in the main study with age ≥50 years.

Exclusion criteria: Those applied for the main study. Additionally, reading difficulties, and non-Spanish or Catalan native speakers will also be excluded.

Baseline cognitive assessment (T0): We selected a battery of tests with input from a neurologist and a neuropsychologist – both experts on cognitive disorders. Two blinded-trained professionals (JP, ML) will perform the cognitive assessment in a quiet

setting. All tests will be performed in the same order: First, the cognitive assessment with the Memory Alteration Test (M@T), which is a validated tool for screening mild amnestic cognitive impairment and early Alzheimer's disease; [21] Second, the digit span forwards and backwards subtests from the Wechsler Adult Intelligence Scale (WAIS-III) to explore attention span (digits forwards) and working memory (digits backward); [22] Third, the Trail Making Test (forms A and B) to measure visual-motor skills, alongside attention, sequencing, and cognitive flexibility; [23] Fourth, the Symbol Digit Modalities Test (SDMT), to assess cognitive processing speed; [24] Fifth, the Semantic Fluency Test, where participants will verbalise as many animals as possible within one minute, and the Phonetic Fluency Test, where participants will verbalise as many words as possible beginning with P, M, and R, to evaluate language and executive functions domains; [25] Finally, we will use the Mini-Mental State Examination (MMSE) as a global cognitive screening tool. Additionally, after the test completion, patients will be queried regarding subjective cognitive complaint by asking "Have you perceived any cognitive problems recently?" and "Have you experienced any memory problems recently?".

Postoperative cognitive assessment (T1):

We will perform a cognitive assessment using the same setting and battery of cognitive tests than the basal assessment at the 3-month postoperative follow-up.

Outcome: The main outcomes of this sub-study will be the incidence of cognitive impairment before surgery and postoperative cognitive disfunction. For the definition of cognitive impairment, we will exclude MMSE. Raw scores from each test will be adjusted to age and years of education using validated Spanish normative data from cognitively unimpaired subjects. [26] Abnormal tests will be those tests with adjusted scores bellow 1 or more standard deviation from cognitively unimpaired subjects. Cognitive impairment will be defined as two or more abnormal cognitive tests. Patients without preoperative cognitive impairment, showing a new cognitive impairment during the 3-month postoperative follow-up will be defined as having postoperative cognitive dysfunction.

Statistical analysis: Randomized groups will be compared for balance on all potentially confounding baseline variables using descriptive statistics and the standardized difference (ASD), which is the difference in means or proportions divided by the pooled standard deviation. Criterion for imbalance will be an absolute standardized difference > 0.10. Any imbalanced baseline variables will be adjusted for in all analyses below. Data transformations will be made, or non-parametric analyses used to meet model assumptions, as appropriate. Analyses will be intent to treat, with a significance level of 0.05. We will assess the efficacy of the prehabilitation program to standard care on the incidence of POCD using either Pearson chi-square test or logistic regression if there is a need to adjust for baseline imbalance in potentially confounding variables. In either case, the relative risk of developing POCD at 3-months after surgery and its 95% confidence interval will be estimated.

Patient and public involvement

Patient and public involvement was taken into consideration for the development of this protocol. A satisfaction questionnaire was given to a sample of patients who had undergone a prehabilitation programme as part of their clinical pathway before an abdominal surgery. They gave feedback about both the assessments and interventions included in this trial. As a result of their feedback we proceeded to reduce the number of questionnaires given during the assessments, as well as an assessment and intervention redesign, resulting in a more flexible schedule for the participants.

- *ETHICS AND DISSEMINATION*

Ethics approval for this trial has been obtained by the Ethics Committee of Clinical investigation of Hospital Clinic de Barcelona (HCB/2017/0708). This trial will be conducted according to the principles emanating from the Helsinki Declaration, with compliance to the Good Clinical Practice and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. Confidentiality for participants and their data will be guaranteed according to the Spanish data protection law 'Ley Orgánica de Protección de Datos de Carácter Personal' (15/1999, 13 diciembre) and the General Data Protection Regulation from the European Union (EU 2016/679).

All the explorations and tests in this trial are considered minimally invasive and are performed in presence of a physician under strict monitoring. The non-pharmacological characteristics of the intervention exclude the need for additional trial insurances.

- *Informed consent*

To avoid contamination among groups, there will be two informed consents: all participants allocated in the control group will be proposed to participate in a study to investigate the relationship between cardiopulmonary reserve and postoperative outcomes and will sign the informed consent for the control group. All participants allocated in the intervention group will be proposed to participate in a study that investigates the effects of a multimodal prehabilitation programme on postoperative outcomes. Patients in the intervention group will sign the intervention group informed consent, where the intervention is defined. All potential participants will be given time to read the informed consent form, consider participation and ask doubts or questions regarding the study participation. If patient agrees to participate, he or she will be asked to provide written consent in the informed consent document. Participants will be free to withdraw their consent and opt out from the trial at any time without needing to explain the reason why. Withdrawal from the trial will not carry any prejudice in the participant care.