PROTOCOL FOR AN INTERVENTIONAL STUDY

Sarcopenia After Cardiac Surgery: An Overlooked Target for Therapeutic Optimization?

STRONG– *Sarcopenia and TRaining Outcomes iN post-cardiac surGery patients*

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Confidentiality Statement

The information in this document is strictly confidential and is available for review to Investigators, potential Investigators and appropriate Ethics Committees, Institutional Review Boards or Competent Authorities.
No disclosure should take place without written authorization from the Sponsor.

SIGNATURES

Title: Sarcopenia After Cardiac Surgery: An Overlooked Target for Therapeutic Optimization?

Protocol: STRONG

The undersigned confirm that the above referenced protocol has been acknowledged and accepted, they agree to conduct the Study in compliance with the approved protocol, and will adhere to: the ICH guidelines, the most recent version of the Declaration of Helsinki, the EU General Data Protection Regulation 2016/679 (GDPR), relevant Belgian laws implementing the GDPR, the Belgian Law of August 22nd 2002 on patient rights, and any other regulatory requirements and Standard Operating Procedures (SOPs), as applicable.

The undersigned agree not to disclose the confidential information contained in this document for any purpose other than the evaluation or conduct of the Study, without prior written consent of the Sponsor.

Coordinating Investigator

Prof Dr. Véronique Cornelissen …… ……

Signature Date

TABLE OF CONTENTS

LIST OF PARTICIPATING SITES ..... **Error! Bookmark not defined.**
SIGNATURES 2
TABLE OF CONTENTS 3
FUNDING AND SUPPORT ..... **Error! Bookmark not defined.**
ROLES AND RESPONSIBILITIES 4
STUDY SYNOPSIS 5
1. Background and Rationale 7
2. Study Objectives and Design 7
2.1 Study objectives 8
2.2 Primary Endpoints 8
2.3 Secondary Endpoints 8
2.4 Study Design 10
2.5 Expected duration of the study 10
2.6 Translational research ..... **Error! Bookmark not defined.**
3. Study Population / Eligibility Criteria 12
3.1 Inclusion criteria 12
3.2 Exclusion criteria 12
4. Assessment of Efficacy 12
5. Assessment of Safety 16
5.1 Specification, timing and recording of safety parameters ..... **Error! Bookmark not defined.**
5.2 Treatment stopping rules 16
6. Statistics and Data Analysis 20
7. Data handling 20
7.1 General data handling information 21
7.2 Study specific data handling information 21
8. Ethical and Regulatory Considerations 23
8.1 Ethics Committee (EC) review & reports 23
8.2 Protocol / GCP compliance 23
8.3 Data protection and participant confidentiality 23
9. Research Registration, Dissemination of Results and Publication Policy 23
10. Insurance/Indemnity 24
11. References 24

ROLES AND RESPONSIBILITIES

The Principal Investigator (PI) is responsible for the conduct of the Study at his/her Participating Site, and for protecting the rights, safety and well-being of Study participants. As such the PI must ensure adequate supervision of the Study conduct at the Participating Site. If any tasks are delegated, the PI will maintain a log of appropriately qualified persons to whom he/she has delegated specified Study-related duties. The PI will ensure that adequate training is provided and documented for all Study staff, prior to conducting assigned Study-related activities. Even when certain activities are delegated, the PI will ultimately remain responsible for the conduct of the Study at his/her Participating Site.

It is the Coordinating Investigator's (CI's) responsibility to supervise the general conduct (e.g. Study progress, communication, protocol training and support of the participating sites, annual reporting to the Ethics Committee (EC), end of Study notification(s) and results reporting…) of the Study. The CI fulfils both Investigator and Sponsor responsibilities, as outlined in International Conference on Harmonisation – Good Clinical Practice (ICH-GCP) E6(R2) and applicable regulations.

PI and CI shall each be referred to as «Investigator(s)».

STUDY SYNOPSIS

Title of clinical Study («Study»)	Sarcopenia After Cardiac Surgery: An Overlooked Target for Therapeutic Optimization?
Protocol Short Title Acronym	STRONG– Sarcopenia and TRaining Outcomes iN post-Cardiac suRGery patients
Sponsor name	UZ Leuven (University Hospital Leuven)
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Co-investigators	Dr. Kaatje Goetschalckx, Dr. Jomme Claes, Prof. Dr. Bart Meyns, Prof. Dr. Wouter Oosterlinck
Medical condition or disease under investigation	Cardiac patients hospitalized following cardiac surgery
Study rationale	Little is known about the prevalence of sarcopenia in patients following cardiac surgery and how it evolves during the post-recovery period. This lack of data limits the development of targeted rehabilitation and preventive strategies. Understanding how muscle mass and function evolve after cardiac surgery is essential to reducing the risk of functional decline, hospital readmissions, and mortality. Early diagnosis and follow-up of sarcopenia in this population could facilitate a more personalized approach to cardiovascular rehabilitation, with specific emphasis on muscle preservation and recovery.
Primary objective	To examine the prevalence of sarcopenia in patients undergoing different types of cardiac surgery in UZ Leuven, and to evaluate the trajectory of muscle mass and function during the postoperative period.
Secondary objective(s)	-To identify clinical and demographic factors associated with the presence of sarcopenia in patients following cardiac surgery. -To assess and understand longitudinal change in spontaneous recovery from sarcopenia between hospital discharge (end of phase I rehabilitation) and the start of phase II ambulatory cardiac rehabilitation. -To evaluate the effectiveness of the current phase 2 ambulatory cardiac rehabilitation program at UZ Leuven in improving muscle mass and function in patients with sarcopenia. -To determine the impact of sarcopenia on long-term clinical outcomes in post-cardiac surgery patients.
Endpoints	Diagnosis of sarcopenia based on assessment of muscle mass and muscle function and functional testing.

Sample size	±300 patients after cardiac surgery
Maximum duration a research subject remains in the study	One year from the day of hospital discharge
Participating research sites	UZ Leuven
Third parties	Not applicable

1. Background and Rationale

The 2021 ESC guidelines for the prevention and treatment of cardiovascular diseases in clinical practice emphasize the importance of proper screening and management of sarcopenia.[1] Sarcopenia is defined as a progressive and generalized skeletal muscle disorder characterized by accelerated loss of muscle mass and function, which is associated with various adverse outcomes including falls, fractures, functional decline, and increased mortality[2]. Although sarcopenia has traditionally been regarded as an age-related syndrome (primary sarcopenia), the condition is not exclusive to older populations. Increasingly, sarcopenia is being identified in younger individuals suffering from specific or multiple chronic diseases (secondary sarcopenia).[2]

Secondary sarcopenia is particularly relevant in patients with cardiovascular disease.[3] For example, in a study done in China, 78 (22.6%) out of the 345 enrolled participants who were hospitalized for coronary heart disease were found to have sarcopenia.[4] Even higher prevalence rates were observed in Brazil where 64.6% and 35.4% of the 99 elderly patients with myocardial infarction presented with sarcopenia and sarcopenic obesity, respectively.[5] Unlike the slow progression observed in primary sarcopenia, secondary sarcopenia can develop acutely, for instance within days following an acute hospital admission, leading to rapid deterioration of muscle mass and function. Acute sarcopenia, lasting <6 months, is typically related to acute illness, injury or hospitalization, and is reversible if appropriate treatment (e.g., exercise, nutrition) is initiated in a timely manner.

Nevertheless, sarcopenia remains frequently underrecognized in current clinical practice among patients recovering from cardiac surgery. Traditional cardiovascular risk assessment does not account for sarcopenia or frailty, instead relying on age and comorbidities as indirect measures. Consequently, sarcopenia is often underdiagnosed. This lack of awareness results in many patients with sarcopenia not being identified in a timely manner, thereby missing opportunities for early and effective intervention.

Further, little is known about the trajectory of sarcopenia during the recovery process following cardiac surgery. While sarcopenia is increasingly recognized as a relevant prognostic factor in cardiac surgical patients, most available research focuses on its prevalence and cross-sectional associations at single time points, often preoperatively or in the early postoperative phase. The changes in muscle mass, strength, and function throughout the rehabilitation period remain poorly characterized.

Understanding the determinants and temporal evolution of sarcopenia in this patient population is of clinical importance for several reasons. First, the postoperative period is characterized by multiple interacting factors that can accelerate or mitigate acute muscle loss, including systemic inflammation, immobilization, nutritional status, metabolic changes, and the presence of comorbidities, leading to acute secondary sarcopenia. Second, the recovery trajectory after cardiac surgery varies between individuals, suggesting that the risk and reversibility of sarcopenia may differ over time. Third, there is currently little understanding of the key predictors of sarcopenia progression or recovery over time. Though, this knowledge would enable the development of early, targeted, and personalized interventions aimed at preserving or restoring muscle mass and function, ultimately improving functional outcomes, quality of life, and long-term prognosis.

Finally, at UZ Leuven, approximately 447 patients eligible for cardiac rehabilitation currently enroll in the program on a yearly basis (data from 2023). The percentage of patients with sarcopenia among this group of patients is unknown. This multidisciplinary program has consistently demonstrated substantial benefits in improving exercise capacity, with mean increases in peak oxygen uptake (VO_2peak) of 20%. However, it remains to be investigated whether the current rehabilitation program is sufficient to improve muscle mass and muscle function in patients with sarcopenia, or whether these patients require a more tailored approach. Given that sarcopenia involves both quantitative and

qualitative deficits in skeletal muscle, and that improvements in aerobic capacity do not necessarily translate into parallel gains in muscle mass or strength, it is plausible that the current rehabilitation may be suboptimal for this subgroup. Addressing this knowledge gap is essential to ensure that rehabilitation strategies are not only effective in enhancing cardiorespiratory fitness but also in reversing or mitigating sarcopenia, thereby maximizing overall functional recovery and long-term prognosis.

2. Study Objectives and Design

2.1 Study objectives

This project overall aim is to comprehensively investigate t**he prevalence, determinants, natural progression, intervention response, and long-term consequences of sarcopenia** in patients undergoing different types of cardiac surgery, in order to inform the development of targeted rehabilitation strategies.

Primary aim: To examine the *prevalence of sarcopenia* (primary and secondary), and *to evaluate the trajectory* of muscle mass and function during the one-year post-operative period in patients following different types of cardiac surgery in UZ Leuven.

Secondary aims:

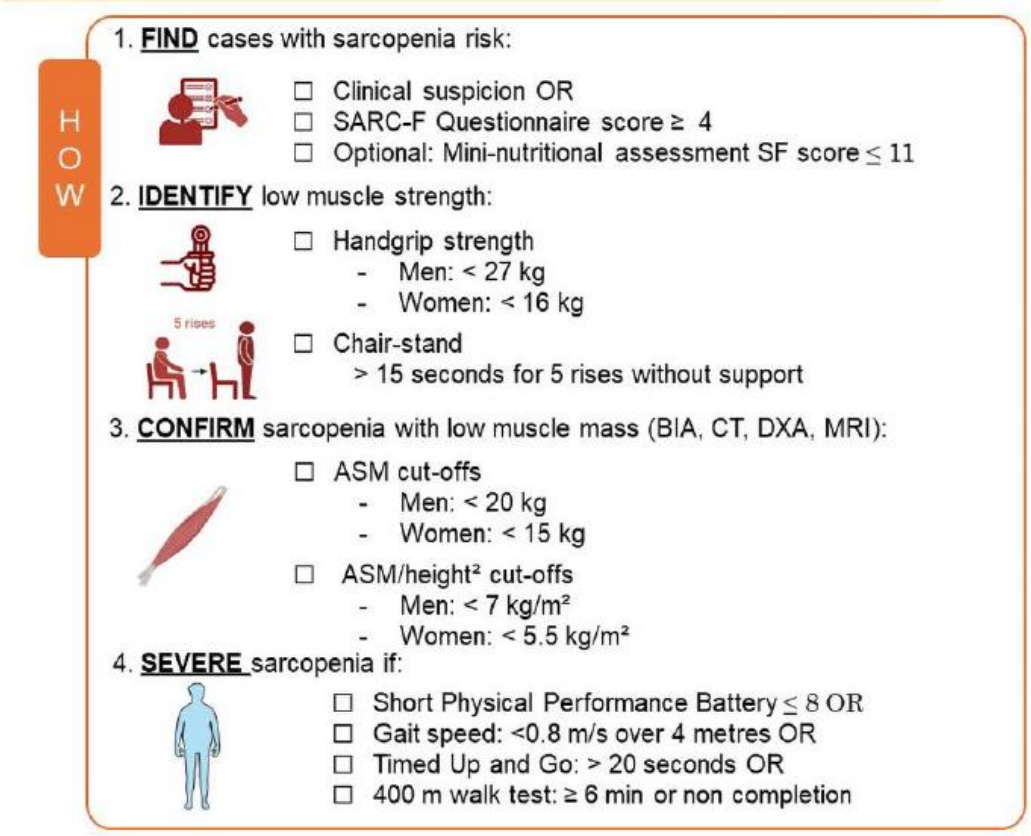
- To identify clinical and demographic factors associated with the presence of sarcopenia in patients following cardiac surgery at different phases in the recovery period.
- To understand longitudinal change in spontaneous recovery from sarcopenia between hospital discharge (end of phase I rehabilitation) and the start of a phase II ambulatory cardiac rehabilitation in patients with acute sarcopenia during hospitalisation.
- The evaluate the effectiveness of the current phase 2 ambulatory cardiac rehabilitation program at UZ Leuven in improving muscle mass and function in patients with/without sarcopenia.
- To determine the impact of sarcopenia on long-term clinical outcomes in post-cardiac surgery patients.

2.2 Primary Endpoints

Our primary endpoint will be the **prevalence of sarcopenia** in patients following cardiac surgery, assessed **at 4 fixed time-points** in the recovery phase from cardiac surgery: i.e. T1 at hospital discharge (end of phase I CR), T2 at initiation of phase 2 ambulatory CR or 4 weeks after hospital discharge, T3 following 3 months of phase II ambulatory CR in patients that engaged in CR at UZ Leuven, and T4 one-year after hospital discharge.

The diagnosis of sarcopenia will be established using the EWGSOP2 criteria[2] (Figure 1) and in line with the recommendations in the recent Scientific Statement of the European Association of Preventive Cardiology of the European Society of Cardiology. [6] A detailed description of the comprehensive set of validated measurement procedures for the evaluation of muscle function, muscle mass, functional performance is provided in section 4.

Figure 1. Screening flow chart for sarcopenia (Cornelissen V et al. EJPC 2025)[6]



2.3 Secondary Endpoints

To investigate the **determinants of sarcopenia**, and the **factors influencing the evolution of sarcopenia** over time the following explanatory factors will be measured as secondary endpoints. An overview of these secondary endpoints is presented in table 1. All secondary endpoints are part of routine clinical care, except the endpoints highlighted in green. A detailed overview of the measurement methods for each of these secondary endpoints is presented below. Patients who will not enroll in cardiac rehabilitation (CR) at UZ Leuven but are diagnosed with sarcopenia at T1 will be invited for a re-assessment at T2. Similarly, patients who still meet the criteria for sarcopenia at T2 will be invited for an additional re-assessment at T3. These assessments constitute additional measurements performed solely for study purposes. Patients with sarcopenia that will enroll in another CR centra will not be invited for re-assessments at T2 and T3.Table 1: Overview of secondary endpoints with timing of assessment

	T1 discharge phase I	T2 initiation phase II	T3 completion phase II	T4 one-year follow-up
Informed consent	X			
Demographics, medical history, medication use	X	X	X	X

Physical activity and sedentary behaviour (IPAQuestionnaire)	X	X	X	X
Health related quality of life (SF36)	X	X	X	X
Anxiety and Depression (HADS)	X	X	X	X
Body composition	X	X	X	X
Nutrition	X	X	X	X
Venous blood sample from KWS	X	X	X	X
Cardiopulmonary exercise test		X Only in patients enrolling in CR	X Only in patients enrolling in CR	X All patients
Implementation outcomes of CR at UZ Leuven	X	X	X	
Serious adverse events	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx			

2.4 Study Design

This study is an **interventional, longitudinal, single-center cohort study** enrolling patients who are hospitalized at UZ Leuven following cardiac surgery and are eligible for cardiac rehabilitation. An overview of the study flow and time points of measurement is presented in Figure 2

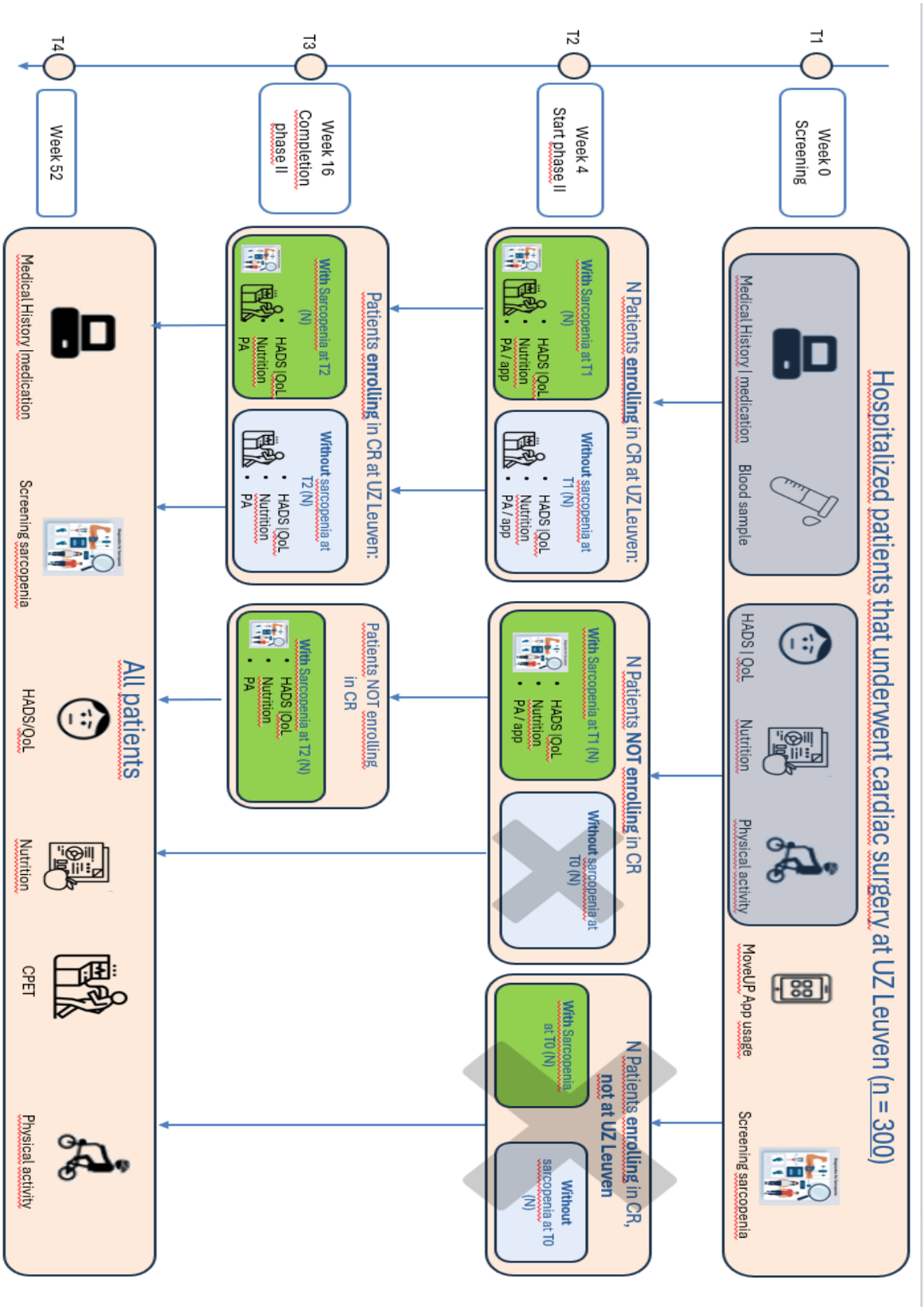


Figure 2. Study flow of the STRONG study

2.5 Expected duration of the study

The follow-up duration for each patient is one-year, starting from the day of hospital discharge.

3. Study Population / Eligibility Criteria

3.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

- Hospitalized following cardiac surgery (i.e. hospitalization unit 18 and 22)
- Stable with regard to symptoms
- Eligible for cardiac rehabilitation according to current guidelines following hospital discharge
- Voluntary written informed consent of the participant has been obtained
- At least 18 years of age at the time of signing the Informed Consent Form (ICF)

3.2 Exclusion criteria

Participants eligible for this study must **not** meet any of the following criteria:

1. Not eligible for cardiac rehabilitation according to current guidelines
2. Unable to perform the physical performance test due to physical or mental issues as up to decision by supervising cardiologist

Treating physiotherapists working on the different wards will be responsible for recruiting the patients and obtaining informed consent.

4. Assessment of Efficacy

4.1 Selection of participants / recruitment

Potential participants will be all patients who are hospitalized at Hospitalization 18 and Hospitalization 22 after cardiac surgery in UZ Leuven. A member of the physiotherapy team responsible for the treatment of these patients after surgery, will perform the initial screening using the 'Klinisch Werkstation' (KWS). This physiotherapist works under the authorization of Prof. Dr. Bart Meyns, who is the medical department head of the department of cardiac surgery within UZ Leuven.

Upon meeting the inclusion criteria, potential participants will be addressed by their treating physiotherapist during their hospital stay at Hospitalization 18 or Hospitalization 22. Potential participants will be briefed on the objectives and expectations of this study. If patients express a voluntary interest in participating in this research, they will be invited to sign the informed consent form. It will be made clear that involvement in the trial does not guarantee any specific benefits and will not impact their current treatment.

Additionally, informative flyers will be utilized to facilitate voluntary enrolment and to communicate effectively with prospective participants. These promotional materials will be disseminated through the relevant departments of the hospital.

Furthermore, a one-page trial overview intended for the medical staff will be distributed. This one-page trial overview will offer information and insights into the study design and objectives, ensuring that the medical professionals involved are well-informed and equipped to support the research project.

4.1.1 Participant consent and withdrawal of consent

The study will be conducted only on the basis of prior informed consent by the study participants and/or their legally authorized representative(s). As such, no study-related procedures will be conducted prior to obtaining written informed consent from potential study participants.

The process for obtaining and documenting initial and continued informed consent from potential study participants will be conducted in accordance with Good Clinical Practice (GCP), applicable regulatory requirements and internal Standard Operating Procedures (SOPs).

All originally signed obtained Informed Consent Forms (ICFs) must be retained/archived in the Investigator Site File (ISF) at the Participating Site and must not be destroyed (even when a scanned copy is available) before expiration of the legal archiving term as defined in the protocol section entitled "Archiving".

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. The participant's request to withdraw from the study must always be respected without prejudice or consequence to further treatment. Consent withdrawal will be documented in the electronic Case Report Form (eCRF).

Study data and samples collected before withdrawal can be used in the study. No new study data or samples will be collected after withdrawal of the participant.

4.1.2 Premature discontinuation of study treatment

Participants may voluntarily discontinue from study and prematurely end their participation in the study for any reason at any time. In such case the Investigator must make a reasonable effort to contact the participant (e.g. via telephone, e-mail, letter) in order to document the primary reason for this decision.

The Investigator may also decide at any time during the course of the study, to temporarily interrupt or permanently discontinue the study participation if it is deemed that continuation would be detrimental to, or not in the best interest of the participant.

A participant should not be considered lost to follow-up until due diligence has been completed.

4.2. Study assessments and procedures

The primary endpoint – sarcopenia – will be diagnosed following the flow chart presented in Figure 2. Therefore, the following measurements will be performed at the 4 timepoints by the treating physiotherapist of the patient:

- The diagnostic process will start with the SARC-F questionnaire (SARC-F). This questionnaire is a practical and accessible self-reported screening tool for sarcopenia, recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2). It consists of five items assessing: muscle strength, assistance in walking, rising from a chair, climbing stairs and Falls. Each item is scored from 0 to 2, yielding a total score ranging from 0 to 10. A score of ≥4 indicated a probable diagnosis and signals the need for further diagnostic assessment. [7] Patients will be asked to complete the SARC-F questionnaire as an online survey in REDcap together with the treating physiotherapist.

- Isometric handgrip strength will be assessed with the patient in seated position. Maximal isometric handgrip force is measured by the Jamar hand dynamometer for both hands. Patients will perform three maximal isometric contractions of 5s per hand. The highest of 3 reproducible attempts is noted as the outcome. Cut-off values: <27 kg for men and <16 kg for women, as recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2)
- Chair stand: This test quantifies the functional lower extremity strength. In this test, patients are asked to complete 5 cycles sit-to-stand as fast as possible from a 45 cm height chair (without armrests). The participant may practice 1 repetition prior commencing the test. A time of >15 seconds to perform 5 repetitions indicates low muscle strength.
- Body composition: (BIA) estimates body composition by measuring the impedance of a low-frequency electrical current passed through the body. BIA offers an optimal balance between affordability and accuracy, making it suitable for routine clinical practice. The EWGSOP2 recommends BIA as a valid method for assessing muscle mass in clinical settings.
- Short Physical Performance Battery (SPPB):

  This test assesses lower extremity function and mobility. It consists of 3 subtests that are scored and points are added up:

  - 4-meter gait speed: To evaluate the patient's functional gait speed. Patients are asked to walk a distance of 4 meters at their own walking speed. The test is repeated twice. The best time of the 2 attempts is used for the rating (17). Cut-off: <0.3 m/s or ≥0.3 m/s.

  - 5 times sit to stand: This test quantifies the functional lower extremity strength. In this test, patients are asked to complete 5 cycles sit-to-stand as fast as possible from a 45 cm height chair (without armrests). Saturation, heart rate, symptom scores for dyspnea and leg fatigue (BORG scale) are assessed at the beginning and at the end of the test. The participant may practice 1 repetition prior commencing the test. The time needed to perform 5 repetitions is noted (18). Cut-offs: ≤11.19 seconds (4 points); 11.20-13.69 seconds (3 points); 13.70-16.69 seconds (2 points); >16.7 seconds (1 point); >60 seconds or unable (0 points).

  - Balance test: In this test, patients take specific positions (side by side stand, semi-tandem stand and tandem stand) for a maximum of 10 seconds after demonstration of each foot position. Progressively the foot positions become more difficult. Patients may use their arms, bend their knees or move their body to maintain their balance but they must not move their legs or cannot hold on to something for support. Each patient who failed a specific position during the first 2 seconds is eligible for one more attempt to pass. If patients can hold a specific position for 10 seconds, they will receive 1 point. If patients cannot hold a specific position for 10 seconds or did not attempt the specific position, they will receive 0 points. Once a specific position cannot be hold for 10 seconds, the balance test will be ended.

  Rating of the SPPB: Each task is scored out of 4 (0: worst performance - 4: best performance), with a total score from the tree subtests ranging from 0 (lower level of function) to 12 (higher level of function).

- Time up and go: This test evaluates functional mobility and fall risk. From a seated position in a standard chair (seat height ~46 cm, with armrests), patients are instructed to stand up, walk 3 m at a comfortable and safe pace, turn, walk back, and sit down. Timing starts on the command "GO" and stops when the patient's back touches the chair. One practice attempt is allowed, followed by one timed attempt; the use of a walking aid is permitted if normally used. The outcome is the time in seconds. Cut-off: ≤10 seconds is considered normal in healthy older adults; ≥13.5 seconds indicates increased fall risk; ≥20 seconds reflects low physical performance and may indicate severe sarcopenia.

Secondary endpoints and their timing of assessment are presented in Table 1

- ***Basic demographic data,* medication and medical history** as well as hospitalization are derived from the participants electronic health record ('KWS'). After verifying these with the patient this information will be collected using an electronic clinical report file (eCRF, Redcap).

- ***Anthropometric measurements*** including height (m) (only at T1), body mass (kg) and waist and hip circumference are measured by the treating physiotherapist during each of the 4 visits.
- ***Physical activity*** and sedentary behaviour will be assessed via the International Physical Activity Questionnaire (IPAQ) which will be administered as a survey via REDcap. The IPAQ assesses self-reported physical activity over the past 7 days, capturing walking, moderate-intensity activity, vigorous-intensity activity, and sitting time. Data are converted to metabolic equivalent minutes per week (MET-min/week) according to standardized scoring. Physical activity is classified as low, moderate, or high.
- ***Nutrition:***

  Mediterranean Diet Adherence Screener (MEDAS):
  The MEDAS is a 14-item questionnaire designed to assess adherence to the Mediterranean dietary pattern. Each item relates to a specific dietary habit or food frequency, with responses scored as 0 or 1 based on predefined criteria. The total score ranges from 0 to 14, with higher scores indicating greater adherence. A score ≥9 is generally considered high adherence, while ≤5 reflects low adherence.

  Mini Nutritional Assessment (MNA):
  The MNA is a validated screening tool for identifying malnutrition or risk of malnutrition in older adults. It consists of 18 items covering anthropometric measurements, general health status, dietary habits, and self-perceived nutrition. The maximum score is 30; ≥24 indicates normal nutritional status, 17–23.5 indicates risk of malnutrition, and <17 indicates malnutrition.

- ***Health-related quality of life and psychosocial well-being***. Beyond its physical consequences, sarcopenia can also significantly affect health-related quality of life (HRQoL), influencing not only self-perceived physical capacity, as assessed by HRQoL tools, but also psychological well-being and social participation. In our study, HRqoL will be assessed using the Short-form 36 (SF-36), whereas psychological well-being will be evaluated by means of the Hospital Anxiety and Depression Scale (HADS). Both questionnaires will be assessed as an online survey via REDcap.

- ***Cardiopulmonary exercise test (CPET).*** As part of the routine care, the patient that enrolls in the phase II ambulatory CR program will undergo a maximal CPET at T2 and T3 to evaluate maximal aerobic capacity and safety of exercise participation. Following recent guidelines, participants will undergo CPET on a sitting cycle ergometer using an individualized ramp protocol (10W + 10W/min or 20W + 20W/min) ensuring a test duration between 8-12 mintues. Electrocardiogram (ECG) monitoring and breath-by-breath gas analysis (VO2, VCO2 and ventilation) will be performed continuously, and blood pressure will be monitored every other minute. Full disclosure ECG tracings and breath-by-breath gas exchange values (stored at 10s resolution) will be monitored and saved for review at rest, during the test, and during the recovery phase. CPETs will be supervised by dr. Kaatje Goetschalckx (head of Cardiac Rehabilitation - UZ Leuven). At one-year FU, all patients will be invited for a CPET.

- **Blood sample.** Blood chemistry results associated with sarcopenia and muscle wasting will be obtained from the standard blood samples collected during the hospitalization of the patients after cardiac surgery and during their recovery period. Outcomes of interest include kidney function measures (eGFR) and waste products generated from muscle metabolism and protein breakdown (creatinine). Furthermore, inflammatory markers (CRP) hemoglobine, hematocrite, white blood cell count, platelets, potassium, kalium, chloride, platelet as part of routine blood sampling

- **Implementation outcomes of CR in UZ Leuven** To evaluate the effectiveness of our current CR program at UZ Leuven on sarcopenia, participants that are eligible for CR will be motivated to enroll in the standard 12 week ambulatory cardiac rehabilitation program of UZ Leuven consisting of 36 supervised exercise sessions at Revalidatie 1(E494) at the University Hospital Leuven (under supervision of dr. Kaatje Goetschalckx). Patients enrolled in the program will

exercise three times per week for approximately 75 minutes per session. Our current CR program includes aerobic exercises on the stationary bicycle, armergometer, treadmill, elliptical trainer and stair climber supplemented with dynamic calisthenics and strengthening exercise using own body weight. Both in the prehabilitation phase before surgery and in the transition phase from phase I to phase II rehabilitation, patients hospitalized at UZ Leuven have the opportunity to use the MOVE up app to maximize fitness before surgery and support recovery after surgery.

- Number (%) of patients with/without sarcopenia who used MOVE UP app before undergoing surgery at UZ Leuven. MOVE UP is an app that is recommended routinely to patients at UZ Leuven prior to cardiac surgery
- Number (%) of patients with/without sarcopenia who used MOVE UP app after surgery at UZ Leuven.
- Number (%) of with/without sarcopenia who enrol in CR at UZ Leuven or at another CR program
- Adoption: Number of patients with/without sarcopenia enrolling in the phase II CR programme at UZ Leuven and completing the CR programme
- Fidelity: % of completed sessions (n/36) within a 3-month period in patients with and without sarcopenia in patients enrolling in CR at UZ Leuven
- Sustainability: the number of patients that is meeting the physical activity guidelines of 150 minutes of moderate to vigorous physical activity at one-year follow-up among patients that enrolled/did not enroll in a phase II CR programme stratified by presence of sarcopenia. Whether a patient is meeting the physical activity guidelines will be evaluated by means of the IPAQ.

- ***Serious adverse events*** (see section 5: assessment of safety)

5. Assessment of Safety

During the one-year follow-up period we will record both adverse and serious adverse events during each contact with the patient.

The following events will be registered in REDcap (see 5.1.3 / 5.1.4)

5.1 Definitions

5.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or subject during the follow-up period
An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE.

5.1.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that results in any of the following:

- Inpatient hospitalisation or prolongation of existing hospitalization
- A persistent or significant disability or incapacity
- A congenital anomaly or birth defect
- A life-threatening[a] experience
- Death
- Important medical events that may be considered an SAE when - based on appropriate medical judgement - they may jeopardise the subject and may require medical or surgical intervention to prevent one of the above outcomes

[a] *The term "life threatening" in the definition of SAE refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it was more severe.*

5.1.3 Adverse Reaction (AR)

An AR is any untoward and unintended response in a participant during an experiment in which a causal relationship between the study intervention and an adverse event is a reasonable possibility.

5.1.4 Serious Adverse Reaction (SAR)

A SAR is an adverse reaction that meets the criteria for a serious adverse event (see definition SAE).

5.2 Adverse Events that do not require reporting

In general, the following should not be reported as AEs:

- Pre-existing conditions, including those found as a result of screening (these should be reported as medical history or concomitant illness). However, in case the pre-existing condition appears to be enhanced by the intervention, this should be reported as an AE.
- Pre-planned procedures, unless the condition for which the procedure was planned has worsened from the first trial-related activity after the subject has signed the informed consent.

The following events are commonly observed and are therefore not considered as adverse events for the purpose of the study:

- Secondary percutaneous intervention after MIDCAB surgery
- Paroxysmal atrial fibrillation

  Although these events should not be reported to the Sponsor, these should be recorded in the patient's medical notes according to routine practice.

The following events not to be considered as SAEs are:

- Pre-planned hospitalisations unless the condition for which the hospitalisation was planned has worsened from the first study-related activity after the subject has signed the informed consent.
- Hospitalisation as part of a standard procedure for protocol intervention. However, hospitalisation or prolonged hospitalisation for a complication of intervention will be reported as an SAE.
- Hospitalisation or prolongation of hospitalisation for technical, practical, or social reasons, in absence of an AE.

5.3 Recording and reporting of Adverse Events

Investigators will seek information on AEs during each patient contact. All events related to the study-specific interventions, whether reported by the patient or noted by trial staff, will be recorded in the (e)CRF within a reasonable time after becoming aware. The diagnosis rather than the individual signs or symptoms should be reported, if available. If no diagnosis is available, the Investigator should record each sign and symptom as individual AEs.

The following minimum information should be recorded for each AE:

- AE description
- start and stop date of the AE
- severity
- seriousness
- causality assessment to the study intervention(s)
- outcome

5.4 Assessment

All AEs must be evaluated by an Investigator as to:

- **Seriousness:** whether the AE is an SAE. See above for the seriousness criteria.
- **Severity:**
  - Severity must be evaluated by an Investigator according to the following definitions:
    - *Mild* – no or transient symptoms, no interference with the subject's daily activities
    - *Moderate* – marked symptoms, moderate interference with the subject's daily activities
    - *Severe* – considerable interference with the subject's daily activities, unacceptable
- **Causality:**
  - *None* – An AE which is not related to the study related interventions.
  - *Unlikely* – An AE for which an alternative explanation is more likely (e.g. concomitant medication(s), concomitant disease(s)), and/or the relationship in time suggests that a causal relationship is unlikely
  - *Possible* – An AE which might be due to the study related interventions. An alternative explanation is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be ruled out.
  - *Probable* - An AE which might be due to the study related interventions. The relationship in time is suggestive (e.g. confirmed by dechallenge). An alternative explanation is less likely.
  - *Definitely* – An AE which is listed as a possible adverse reaction and cannot be reasonably explained by an alternative explanation. The relationship in time is very suggestive (e.g. it is confirmed by dechallenge and rechallenge).

5.5 Timelines for reporting

- After informed consent has been obtained and after initiation of study-related interventions:
  - **All AEs and SAEs causally related to a study-related intervention** will be reported until last follow-up visit.

  - SAE details will be reported by the Investigator to the Sponsor within 24 hours of the study staff becoming aware of the event.:
    - By completing the SAE form in the (e)CRF
- The sponsor will keep detailed records of all AEs reported to him by the investigators.
- When reporting adverse events to the sponsor, the investigator will protect confidentiality by excluding the names of individual subjects, personal identification numbers (e.g. social security numbers) or addresses. The unique code number assigned to the study subject will be used in the report and the investigator retains the code to facilitate data verification by the sponsor and any medical follow-up which may be warranted. The name of the investigator reporting the adverse events will be stated.
- After the study has been completed or terminated, all recorded adverse events will be listed, evaluated and discussed in the final report.

5.5.1 Death

Deaths of subjects who were participating in the study at the time of their death will be reported to the Sponsor without delay (irrespective of whether the death is related to disease progression, study procedure or is an unrelated event). The Sponsor will notify all deaths, as soon as possible after becoming aware, to the Central EC.

5.6 Reporting requirements to the Ethical Committee

The Investigator is responsible for ensuring that all safety events are recorded in the (e)CRF and reported to the Sponsor in accordance with instructions provided below.

The Sponsor will promptly evaluate all SAEs against medical experience to identify and expeditiously communicate possible new safety findings to the Investigators.

5.6.1 Annual reporting

The Sponsor has the obligation to, once a year throughout the study (or on request), submit a progress report to the EC containing an overview of all SAEs occurred during the reporting period, taking into account all new available safety information received during the reporting period

5.6.2 Overview reporting requirements

	WHAT	HOW	TO	TIMELINES
Investigator	AR	AE form	sponsor	as defined in protocol
	SAR	SAE form	sponsor	Immediately (within 24 hours of becoming aware of the event) Exceptions: as defined in protocol
	death	SAE form	sponsor	asap
Sponsor	death	SAE form + narrative	Ethics Committee	asap
	Annual Progress Report	APR template	Ethics Committee	annually

6. Statistics and Data Analysis

Sample size determination

As this is largely part of routine clinical care (except for some exploratory variables), we aim to achieve a convenient sample size of ± 300 patients (200 enrolled in phase II ambulatory CR and 100 not participating). Given that approximately 1500 cardiac surgery procedures are performed each year and 447 patients enroll in the phase II ambulatory CR program at UZ Leuven, this number is deemed achievable during a 1 year inclusion period.

Statistical analysis

All patients with at least the baseline visit will be included in the analyses.

1. Prevalence rates

Prevalence of sarcopenia among patients undergoing cardiac surgery will be calculated as the number of cases fulfilling EWGSOP2 criteria divided by the number of cases not fulfilling these criteria at each of the the four different time points. Additionally, sarcopenia rates will be calculated separately for different pathology groups (i.e. higher in specific patients groups) and per CR enrollment status (is sarcopenia affecting likelihood to enroll in CR). To assess differences of sarcopenia prevalence between the subgroups at the different timepoints, a Chi-squared test will be performed. To assess the change in sarcopenia prevalence within the groups over time, a McNemar or Cochran's Q-test will be used. To assess within-group, between-group and group*time interaction effects a mixed-effects logistic regression will be used.

2. Descriptive data

Anthropometric and medical and functional outcome data (e.g. age, sex, sarcopenia (Y/N), type of cardiac surgery, body composition, blood sampling, functional tests) will be presented as mean ± standard deviation or median and range, depending on the distribution of the data. Comparative analyses will be performed at every timepoint between patients participating in phase II ambulatory CR and those not participating. A mixed-model ANOVA will be performed to calculate within-group, between-group and time*group interaction effects. Post-hoc tests will be conducted in case of significant interaction effects. Analysis will be performed using R software.

3. Possible determinants of sarcopenia and of longitudinal changes in sarcopenia will be investigated by bivariable and multivariable analyses

Determinants of sarcopenia and change in sarcopenia status will first be exploratively evaluated using correlations. The drivers of change in sarcopenia status over time will then be assessed using a mixed-effects logistic regression model with a subgroup of the determinants added as covariates in the model. Covariates to be added in the model will be determined based on clinical relevance and multicollinearity analysis.

4. Longitudinal cluster analyses will be used to explore distinct subgroup trajectories on functional changes over time

Unsupervised machine learning approaches will be used to cluster (density based clustering e.g. K-means, hierarchical clustering) patients based on the change of functional outcomes present in the sarcopenia screening flow (figure 1) and CPET results. The most suited number of clusters will be determined by using a combination of different cluster validity indexes (silhouette score and Dunn index score). The outcome

variables will be compared between the clusters using appropriate statistics depending on the generated number of clusters.

7. Data handling

7.1 General data handling information

Data collection, handling, processing and transfer for the purpose of this Study will be performed in compliance with applicable regulations, guidelines for clinical studies and internal procedures. It remains the responsibility of the Investigator to check that all data relating to the Study, as specified in the Study protocol, are entered into the electronic Case Report Form ((e)CRF) in accordance with the instructions provided and that the forms are filled out accurately, completely and in a timely manner.

(e)CRFs are provided by the Sponsor for each participant. The Study data will be transcribed from the source records into an (e)CRF by Study Staff.

The (e)CRFs shall under no circumstances capture personal data such as but not limited to the participant or their relative(s) name, home address, contact details, full date of birth medical record number (e.g. UZ Leuven EAD number), social security number etc.

7.2 Study specific data handling information

REDCap will be used for electronic data capture and database management. Each participant will be assigned a unique participant identification code which will be used on all case report forms and in the electronic REDCap database. To comply with most recent EU regulations regarding data privacy, personal data collected in this trial will be pseudonymized and protected from any commercial application.

The following datatypes will be collected and/or generated and/or (re)used during the research project:
Reuse: demographic data (e.g. gender), clinical data (e.g. medication, reason for hospitalisation, hospital stay, medical history, biochemistry via KWS)

Collect: Informed consent, physiological data (e.g. CPET, blood pressure, physical activity data, body composition data, functional performance, handgrip strength, questionnaire data). Data will be stored as software-specific files (.doc, XLSX, CSV,..)

Generate: REDCAP (Research Electronic Data Capture) database.

Final databases and raw datafiles will be stored on secure KU Leuven servers, shielded by a 2-factor authentication procedure. Jomme Claes and Prof Cornelissen will be responsible for data management. A separate list of participants linking them to their patient identification code in REDCap will be stored within a KU Leuven server protected by a 'Digital vault for private data' service, compliant with the privacy law and strict rules of data access. We will also use KU Leuven's research data repository service to assure secure, long-term storage, including regular backups. Only authorized users can access the data. All the involved researchers have successfully completed an ICH-GCP course prior to involvement in the proposed project in accordance with the obligations for research staff at KU Leuven. This course included training on responsible conduct of research, informed consent, privacy and research data management.

7.3 Legal requirements

All source data will be kept at a secured location with restricted access at all times. These data must be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data protection laws and regulations and more in particular the EU General Data Protection Regulation 2016/679 (GDPR) and relevant national laws implementing the GDPR. Appropriate technical and organizational measures to protect the data against unauthorized disclosure or access, accidental or unlawful destruction, or accidental loss or alteration must be established. Trial staff whose responsibilities require access to personal data agree to keep the data confidential.

The Investigator and the Participating Site(s) (as applicable) shall treat all information and data relating to the Trial disclosed to them as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the objectives of the Trial as described in this protocol. The collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with applicable laws and regulations regarding personal data protection and the processing of personal data.

The Investigator will maintain all source documents and completed (e)CRFs that support the data collected from each Trial participant, and will maintain a Trial Master File (TMF)/Investigator Site File (ISF) containing all Trial documents as specified in ICH-GCP E6(R3) Chapter 8 entitled "Essential Documents for the Conduct of a Clinical Trial", and as specified by applicable regulatory requirement(s). The Investigator will take appropriate measures to prevent accidental or premature destruction of these documents.

Transfer of the pseudonymized data will be performed via a secured method of transfer taking into account all applicable security arrangements and regulations (such as the European General Data Protection Regulation). The receiving party will be bound by contractual agreement to keep the transferred data confidential at all times and to only process the data for the purpose of the Trial. To this end, appropriate Data Transfer Agreements (DTAs) will be established.

7.4 Audits and Inspections

The Investigator will permit direct access to Trial data and documents for the purpose of monitoring, audits and/or inspections by authorized entities such as but not limited to: the Sponsor or its designees and competent regulatory or health authorities. As such (e)CRFs, source records and other Trial related documentation (e.g. Investigator Site File, the Trial Master File, pharmacy records, etc.) must be kept current, complete and accurate at all times.

7.5 Monitoring

In accordance with ICH-GCP E6(R3) the Sponsor is responsible for monitoring the Trial to ensure compliance with GCP and current legislation, and to verify, among other requirements, that proper written informed consent has been obtained and documented, that the Trial procedures have been followed as shown in the approved protocol, and that relevant Trial data have been collected and reported in a manner that assures data integrity. To this end Source Data will be compared with the data recorded in the (e)CRF. A risk-based approach will be applied to determine the extent of monitoring activities and monitoring of the Trial will be performed by qualified individuals (independent from the site Trial staff), as applicable.

The Sponsor and Investigator/Participating Site will permit direct access to the Trial data and corresponding Source Data, and to any other Trial related documents or materials to verify the accuracy and completeness of the data collected. More details about the monitoring strategy are described in the Trial specific Monitoring Plan (MP).

7.6 Archiving

As specified in ICH-GCP E6(R3) section 8.1 Addendum, the Sponsor and Investigator/Participating Site will maintain a record of the location(s) of all respective Essential Trial Documents (including but not limited to Source Documents, completed and final (e)CRF and ISF/TMF). The Sponsor should ensure that the Investigator has control of and continuous access to the (e)CRF data reported to the Sponsor during the Trial.

The Investigator/Participating Site should have control of all Essential Documents and records generated by the Investigator/Participating Site before, during and following termination of the Trial.

The Sponsor is responsible for archiving Trial specific documentation (such as but not limited to the Trial protocol, any amendments thereto, the final Clinical Study Report (CSR) and the Trial database) according to ICH-GCP E6(R3). Source data and site-specific Trial documents (such as but not limited to the original signed ICFs) will be archived by the participating site(s) according to local practice, and for at least 25 years

following termination of the Trial. Archived data may be held on electronic record, provided that media back-up exists, hard copies can be obtained, if required and measures are taken to prevent accidental or premature loss or destruction of data. Destruction of Essential Documents prior to, during or upon completion of the required archival period, will require written authorisation from the Sponsor.

8. Ethical and Regulatory Considerations

8.1 Ethics Committee (EC) review & reports

Before the start of the Study, this protocol and other related documents will be submitted for review to the EC for Study authorization. The Study shall not commence until such approvals have been obtained and until other relevant essential Study documents, such as duly signed contract agreements, evidence of adequate Study financing etc. are in place.

8.2 Protocol / GCP compliance

The Study must be performed in accordance with the protocol, current ICH and ICH-GCP guidelines, and applicable regulatory and country-specific requirements. ICH guidelines are an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human participants. Compliance with this standard provides public assurance that the rights, safety, and well-being of Study participants are protected, consistent with the principles that originated in the most recent version of the Declaration of Helsinki, and that the Study data are credible, reliable and reproducible.

8.3 Data protection and participant confidentiality

The Study will be conducted in compliance with the requirements of the EU General Data Protection Regulation 2016/679 (GDPR), and the relevant Belgian laws implementing the GDPR including the Belgian Privacy Act of 30 July 2018 on the protection of privacy in relation to the processing of personal data. Any collection, processing and disclosure of personal data, such as participant health and medical information is subject to compliance with the aforementioned personal data protection laws (cfr. Data Processing Annex (DPA) in Appendix). In case personal data is transferred outside the European Economic Area, safeguards will be taken by the Sponsor to ensure that appropriate protection travels with the data in accordance with the GDPR. (https://ec.europa.eu/info/law/law-topic/data-protection/international-dimension-data-protection/rules-international-data-transfers_en#documents)

Any personal data shall be treated as confidential at all times including during collection, handling and use or processing, and the personal data (including in any electronic format) shall be stored securely at all times and with all technical and organizational security measures that would be necessary for compliance with EU and national data protection legislation (whichever is more stringent). The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access thereto or disclosure thereof or loss or destruction while in its custody.

9. Research Registration, Dissemination of Results and Publication Policy

The Declaration of Helsinki (latest version) and European and Belgian regulations require that every research Study involving human participants be registered in a publicly accessible database before recruitment of the first participant. The CI is responsible for registering the Study.

In addition, the CI will fulfil their ethical obligation to disseminate and make the research results publicly available. As such the CI is accountable for the timeliness, completeness and accuracy of the reports. Researchers, authors, Sponsors, editors and publishers must adhere to accepted guidelines for ethical reporting. Negative and inconclusive, as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in publication.

10. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance."

11. References

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7. Malmstrom, T.K. and J.E. Morley, *SARC-F: a simple questionnaire to rapidly diagnose sarcopenia.* J Am Med Dir Assoc, 2013. **14**(8): p. 531-2.