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INPACT: Implementation of Nutritional support and Physical Activity during Cancer Treatment

1. General information

Implementation of Nutritional Support and Physical Activity during Cancer Treatment (INPACT)

Prospective interventional study investigating the implementation of a combined nutritional and physical prehabilitation and rehabilitation program during cancer treatment.

AZGS-number: AZGS2026054

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1.1. Signature page

I have read this protocol in its entirety and I agree to all aspects.

Principal investigator

Signature: Date:

_____ _____

2. Abbreviations

AE	Adverse Event
BMI	Body Mass Index
BORG	Borg Rating of Perceived Exertion Scale
CCI	Comprehensive Complication Index
CPET	Cardiopulmonary Exercise Test
CRF	Case Report Form
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30
EQ-5D	EuroQol 5 Dimensions
GCP	Good Clinical Practice
GP	General Practitioner
HR	Heart Rate
HRQoL	Health-Related Quality of Life
CRP	C-reactive Protein
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	Interleukin
IMP	Investigational Medicinal Product
INPACT	Implementation of Nutritional Support and Physical Activity during Cancer Treatment
ITT	Intention-To-Treat

KWS	Electronic medical record (Klinisch Werk Station)
MRI	Magnetic Resonance Imaging
PG-SGA SF	Patient-Generated Subjective Global Assessment – Short Form
PI	Principal Investigator
PROs	Patient-Reported Outcomes
REDCap	Research Electronic Data Capture
SAE	Serious Adverse Event
TNF	Tumour Necrosis Factor
VO2Max	Maximum oxygen uptake
WBC	White Blood Cell Count
6MWT	6-Minute Walk Test

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4. Protocol synopsis (English)

Title of the study	Implementation of Nutritional Support and Physical Activity during Cancer Treatment (INPACT)
Study design	This study is a prospective, interventional, monocenter, randomised controlled trial to evaluate the implementation of a new care pathway using a pre- and rehabilitation program.
Study Population	Adult patients undergoing oncologic surgery, with a focus on patients scheduled for abdominal (liver) tumour surgery. 103 patients are planned to be included.
Inclusion criteria	• Age ≥18 years • Diagnosed with a primary liver cancer or metastases of the liver. • Patients who need elective surgery (resection) • Understanding and able to write Dutch or French • Able and willing to provide written informed consent
Exclusion criteria	• Paralytic or immobilised patients who are not able to perform exercises • Patients scheduled for an ablation • Kidney dialyse • Impossibility to wait for 4/5 weeks for elective surgery • Underlying medical conditions or orthopedic impairments which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study • Logistic reasons preventing the patient to participate in the pre- and rehabilitation program. • Unable to perform 6 MWT • Active cardiac ischemia
Setting	Patients are planned to be included between October 2026 and April 2028. The INPACT trial is a randomised controlled superiority trial. Patients will be actively followed for approximately 12 weeks (depending on the take-off of the exercise scheme and surgery). Thereafter, patients will be followed up till 3 years post-surgery to determine the 3-year disease free survival.
Intervention	Included patients participate in a four-week prehabilitation program consisting of home-based and in-hospital physical training. Thereafter, patients undergo oncologic surgery according to standard clinical practice. Postoperatively, patients continue home-based and in-hospital rehabilitation. Follow-up

	assessments of physical performance, nutritional status, and patient-reported outcomes are performed up to approximately 6 weeks after surgery.
Control	Patients included in the control group will be followed according to standard of care.
Primary objective	The primary objective of this study is to evaluate if a multimodal prehabilitation program can improve functional capacity in patients scheduled for oncologic hepatic surgery.
Endpoints	The primary endpoint is to compare the patient's functional capacity presurgery (4 weeks after baseline), measured by the 6 minute walk test, between the intervention and usual care group. Secondary endpoints include, amongst others, changes in physical performance, nutritional status, and patient-reported outcomes throughout the perioperative trajectory.
ClinicalTrials.gov number	##

5. Protocol synopsis (Dutch)

Studie titel	Implementatie van voedingsondersteuning en fysieke activiteit tijdens de behandeling van kanker (INPACT studie)
Studie opzet	Prospectieve interventionele studie naar de implementatie van een gecombineerd programma voor prehabilitatie en revalidatie op het gebied van voeding en lichaamsbeweging tijdens de behandeling van kanker.
Studie populatie	Volwassen patiënten die een oncologische operatie ondergaan, met name patiënten bij wie een operatie aan een tumor in de buik (aan de lever) is gepland. 103 patiënten zullen worden geïncludeerd in het onderzoek, gelijkmatig verspreid over de interventie groep en de standaard zorg groep.
Inclusie criteria	• Leeftijd ≥ 18 jaar • Gediagnosticeerd met een primaire leverkanker of levermetastasen • Patiënten die een geplande (electieve) chirurgische resectie dienen te ondergaan • De Nederlandse of Franse taal begrijpen en kunnen schrijven

	• In staat en bereid om schriftelijke geïnformeerde toestemming te geven
Exclusie criteria	• Paralyse of geïmmobiliseerde patiënten die niet in staat zijn om oefeningen uit te voeren • Patiënten die gepland zijn voor een ablatieprocedure • Nierdialyse • Onmogelijkheid om 4 tot 5 weken te wachten op een electieve chirurgische ingreep • Onderliggende medische aandoeningen of orthopedische beperkingen die volgens de onderzoeker een onaanvaardbaar risico vormen voor deelname aan de studie • Logistieke redenen die deelname aan het prehabilitatie- en revalidatieprogramma verhinderen • Niet in staat om de 6-Minuten Wandeltest (6MWT) uit te voeren • Actieve cardiale ischemie

Setting	Patiënten zullen tussen oktober 2026 en april 2028 geïncludeerd worden in de studie. De INPACT-studie is een gerandomiseerde, gecontroleerde superioriteitsstudie. Patiënten worden gedurende ongeveer 12 weken actief gevolgd (afhankelijk van de start van het trainingsprogramma en de operatie). Daarna worden de patiënten tot 3 jaar na de operatie gevolgd om de 3-jaars ziektevrije overleving vast te stellen.
Interventie	De patiënten volgen een prehabilitatieprogramma van vier weken, bestaande uit fysiotherapie thuis en in het ziekenhuis. Daarna ondergaan de patiënten een oncologische operatie volgens de gangbare klinische praktijk. Na de operatie zetten de patiënten de revalidatie thuis en in het ziekenhuis voort. Tot ongeveer zes weken na de operatie worden follow-up visites uitgevoerd van de fysieke prestaties, de voedingsstatus en de door de patiënt gerapporteerde uitkomsten.
Controle	Patiënten die in de controlegroep zijn ingedeeld, zullen worden gevolgd volgens de standaardbehandeling.
Primair Objectief	Evalueren of de implementatie van een prehabilitatieprogramma de functionele capaciteit kan verbeteren bij patiënten waarbij een oncologische leveroperatie is gepland.
Eindpunten	Het primaire eindpunt is het vergelijken van de functionele capaciteit van de patiënt voor de operatie (4 weken na baseline), gemeten aan de hand van de 6-minuten-wandeltest, tussen de interventiegroep en de groep die de gebruikelijke zorg ontvangt. Secundaire eindpunten zijn onder meer veranderingen in fysieke prestaties, voedingsstatus en door de patiënt gerapporteerde uitkomsten gedurende het gehele perioperatieve traject.
ClinicalTrials.gov nummer	##

6. Background and rationale

6.1. Literature

In 2020, nearly 70,000 new cancer diagnoses were made in Belgium—just over 35,000 cases in men and just under 32,000 in women. It has been demonstrated that physical activity significantly reduces the risk of developing several cancer types (1,2). Physical activity is also associated with a lower risk of cancer recurrence and cancer-specific mortality (3–5). In recent years, the scientific literature has shown a growing number of publications on "prehabilitation" in patients with cancer.

Prehabilitation is a complex, multidisciplinary process aimed at optimizing patients' physical condition between the time of cancer diagnosis and the day of treatment (most commonly surgery or chemotherapy).

The three pillars of prehabilitation are:

- optimizing nutritional status (nutrition)
- physical activity or physiotherapy
- psychological support and assistance with coping mechanisms following a cancer diagnosis

In addition, the management of pre-existing comorbidities should be optimized as much as possible, and any dependence on tobacco and alcohol should be addressed (6).

Over the past two decades, an increasing amount of research has focused on strategies to prevent postoperative complications and to mitigate the adverse effects of cancer treatments (systemic therapy or chemotherapy). Prehabilitation aims to improve the patient's functional capacity and nutritional status in order to promote postoperative recovery. Two recently published randomized studies report a 50% reduction in complications after prehabilitation in high-risk patients undergoing major abdominal oncological surgery (7,8). Improved cardiorespiratory fitness at the time a patient must undergo surgery or chemotherapy increases the patient's physiological reserve and enhances their ability to withstand the physical stress associated with surgery or systemic therapy (9).

In addition to the literature demonstrating that prehabilitation may reduce complications, facilitate recovery, and shorten hospitalization, several publications in recent years have also reported improved disease-free survival, as well as lower recurrence rates, in patients who underwent prehabilitation (10–12).

In 50% to 80% of patients with a cancer diagnosis, some degree of malnutrition is present, as demonstrated in multiple studies (13). The severity of malnutrition is often proportional to the stage of the cancer, but it is also frequently associated with specific cancer types. For example,

patients with pancreatic tumours or oesophageal tumours are very often in a state of cachexia. Despite these figures, a relatively recent review showed that nutritional screening is performed in fewer than 40% of published studies, and that in most studies this screening is based on non-validated screening methods (14). In patients with locally advanced rectal tumours, a large multicentre observational study recently demonstrated that sarcopenia and hypoalbuminaemia are negatively associated with tumour response to preoperative chemoradiotherapy (15). In contrast, other research indicates that prehabilitation may lead to improved tumour regression after neoadjuvant chemoradiotherapy in locally advanced rectal cancer (16). Loss of muscle mass—whether or not accompanied by loss of fat mass—in patients with cancer is also a predictive factor for postoperative complications and mortality (17,18). A core component of an advanced prehabilitation programme should therefore be to perform a nutritional screening and evaluation for every patient, both clinically and based on imaging that has already been obtained. In addition, DEXA scanning (dual-energy X-ray absorptiometry) can be used to determine fat mass, fat-free mass, and bone density. Most patients with cancer also have conventional imaging in the form of CT or MRI, which can be leveraged, among other assessments, to evaluate the psoas muscle.

6.2. Rationale

In European expert centres, approximately 30% of all liver operations are performed by minimally invasive laparoscopy (19). In az groeninge, approximately 76% of liver resections are performed laparoscopically, and since the introduction of robotic liver surgery this figure has currently risen to 89%. As a result, the median length of stay in az groeninge has been reduced to 3 days (20). In recent years, more and more evidence on prehabilitation has arisen on how we can better prepare patients for surgery. By combining new surgical techniques such as robotic surgery with a robust prehabilitation pathway, we can ensure that patients arrive in better condition “at the start” and can also progress through the entire recovery and healing process more smoothly, with a lower risk of complications.
Functional capacity is a strong determinant of postoperative outcomes and reflects a patient’s physiological reserve before surgery (9). As multimodal prehabilitation primarily aims to optimise a patients’s physcial condition before treatment, improvement in functional capacity represents the most direct and measurable effect of the intervention (6). Following the diagnosis of hepatic cancer, the interval between diagnosis and surgery usually comprises several weeks, providing an ideal window for the implementation of a multimodal prehabilitation programme

Although improved functional capacity has been associated with reduced postoperative morbidity, enhanced recovery, and shorter hospital stay, these outcomes are influenced by multiple perioperative factors (9,22). Therefore, this study is primarily designed to evaluate the direct impact of prehabilitation on functional capacity, while postoperative complications and recovery outcomes are evaluated as important secondary endpoints.

With the INPACT prehabilitation project, az groeninge takes the first step towards becoming a centre of excellence for prehabilitation. The aim of the INPACT trial is to determine the effect of a multimodal pre- and rehabilitation program on functional capacity, next to quality of life and nutritional status.

7. Study objectives and outcome measures

7.1. Primary objective

The primary objective of this study is to evaluate if a multimodal prehabilitation program can improve functional capacity in patients scheduled for oncologic hepatic surgery.

7.2. Secondary objectives

The secondary objectives are:

1. To investigate if an exercise program improves cardiorespiratory fitness and the following physical outcomes: VO2Max, upper and lower body strength
2. To investigate the effect of a multimodal pre- and rehabilitation program on Health-related Quality of life (HRQoL)
3. To investigate if multimodal pre- and rehabilitation program can decrease complications
4. To investigate the effect on nutritional status
5. To investigate the safety
6. To investigate the study compliance
7. To determine the three-year disease-free and overall survival
8. To investigate the implementation of a multimodal pre- and rehabilitation program
9. To investigate the physical activity level of patients in the standard of care group during study participation (IPAQ-SF)

7.3.Explorative objectives

1. To explore the health-economic impact of a multimodal pre- and rehabilitation program.
2. To explore the effect of a multimodal pre- and rehabilitation program on blood markers of inflammation.
3. To explore the effect of breathing exercises

7.4. Primary endpoint

The primary endpoint is to compare the patient's functional capacity presurgery (4 weeks after baseline), measured by the 6-minute walk test, between the intervention and usual care group.

7.5. Secondary endpoints

The secondary outcomes are:

1. Change in distance (cm) on the 6MWT from baseline until V2, and from baseline until V5. Compare the hand grip strength, Vo2max, Biodex lower quadrant, Single leg calf raises, sit-to-stand test, 6MWT at the different timepoints between the two groups
2. PROMs for HRQoL (EORTC QLG Core Questionnaire (EORTC QLQ-C30), EQ5D)
3. Comprehensive Complication Index Score (CCI) and length of hospital stay
4. Nutritional status measured by the PG-SGA SF and compliance of nutritional supplements intake
5. Safety: total number of AEs and SAEs, and proportion of patients with a(n) (S)AE
6. Study compliance: a BORG scale will be completed by patients. Patients will complete an exercise diary to measure the training compliance.
7. Proportion of patients who achieve a 3-year disease-free survival and a 3-year overall survival, compared between the two groups
8. Patients' perceptions will be determined on the implementation of the training program (semi-structured interviews).

7.6.Exploratory outcomes

1. An exploratory health economic analysis will be carried out.
2. Laboratory outcomes: CRP, WBC, IL-6, IL-8, IL-10, TNF-α, troponin, Ferritin, Albumin
3. Patients' perceptions will be determined on the effect of the breathing exercises (semi-structured interviews)

8. Study design and setting

INPACT is a monocenter, open-label, prospective, randomised controlled superiority trial to evaluate the impact of a newly introduced care pathway. Adult patients who are diagnosed with a primary liver cancer or metastases of the liver and in need of an oncologic surgery are eligible. Patients are 1:1 randomised either to the intervention group: a multimodel pre- and rehabilitation program, or standard of care (no formal exercise advice). Patients will be stratified based on chemotherapy (if it is part of the patients treatment plan, binary: yes/no), type of resection (major liver resection or minor liver resection), surgical approach (open vs. minimally invasive (laparoscopic or robotic)), and ejection fraction (binary: <50% (reduced systolic function) or ≥50% (preserved systolic function)).

Randomisation

INPACT is an open-label trial; thus, no blinding procedures will be involved. At baseline, participants will be 1:1 randomised to either the intervention arm (pre- and rehabilitation program) or the usual care arm. A randomisation tool will be incorporated within the web-based platform Research Electronic Data Capture (REDCap), which is also used as electronic case report form (eCRF). A random allocation sequence in blocks of 2 or 4 will be generated by an independent person, using a free-access online tool (https://www.sealedenvelope.com), and is concealed from the study team within the REDCap environment.

Blinding

Due to the nature of the intervention, no blinding is possible.

9. Study population

A total of 103 patients are planned to be included. We estimate to include patients between October 2026 and April 2028 (inclusion period of 1.5 year).

9.1. Inclusion criteria:

Patients enrolled in the study must meet the following inclusion criteria:

- Age ≥18 years
- Diagnosed with a primary liver cancer or metastases of the liver.
- Patients who need elective surgery (resection)
- Understanding and able to write Dutch or French
- Able and willing to provide written informed consent

9.2. Exclusion criteria:

Patients will be excluded from participating in the study if they meet any of the following exclusion criteria:

- Paralytic or immobilised patients who are not able to perform exercises
- Patients scheduled for an ablation
- Kidney dialyse
- Impossibility to wait for 4/5 weeks for elective surgery
- Underlying medical conditions or orthopedic impairments which in the opinion of the investigator places the patient at an unacceptable risk for participation in the study
- Logistic reasons preventing the patient to participate in the pre- and rehabilitation program.
- Unable to perform 6 MWT

- Active cardiac ischemia

10. Study procedures

Patients will be actively followed for approximately 12 weeks (depending on the planning of the cardiologic consultation, surgery, and start of the training scheme), from baseline until 6-weeks post-surgery. After three years, the disease-free survival will be determined. During this 3 years, patients will be followed according to usual care and no additional information will be collected.

After signing the ICF, patients will have a consultation at the cardiology department to determine the patient's capacity to undertake the exercises and whether the patient is able to participate in the exercise program. During this consultation, the participant will have an ECG, echocardiography, and an exercise ECG.

Baseline Assessment

At baseline, patients will be randomised to either the standard of care group or the intervention group. The patient's physical, nutritional, and mental status will be assessed at baseline.

Baseline data include:

- Physical parameters: body weight, height, blood pressure, heart rate, oxygen saturation, muscle strength, and relevant blood values
- Mental parameters: emotional and general well-being, quality of life
- Nutritional parameters: nutritional status questionnaire

The patient will have a Pre/rehab test at V1 consisting of:

- Condition tests:
  - VO2Max test using CPET
  - 6 MWT
- strength tests
  - Biodex lower quadrant
  - Single leg calf raises
  - Hand grip strength
  - Sit to stand (time)

This pre/rehab test will be repeated for all patients at V2, V4 and V5.

These data serve as reference values for subsequent observations during the perioperative trajectory.

Surgery

All patients undergo oncological surgery according to standard clinical protocols and at the discretion of the surgeon. All patients will have the surgery within the same hospital (az groeninge, Kortrijk). No study-specific procedures are performed during the surgery. Perioperative clinical data are collected as part of routine care.

Standard of care group:

Patients randomised to the standard of care group will be followed according to current daily practice. According to standard of care, patients will be advised to walk and be active. However, these patients will not receive formal exercise advice [21].

After surgery, all patients receive standard postoperative care according to local clinical practice. It is standard of care that patients have a dietary consult during hospitalisation, while additional dietary consultations are provided based on the patient's needs. Postoperative recommendations regarding nutrition, physical activity and mobilisation are provided by the treating healthcare team. These recommendations are communicated both verbally and through a standardized patient information brochure. The brochure contains practical advice on postoperative recovery, physical activity and nutritional support and is provided to all patients errespective of study allocation. The patient information brochure has been included as an appendix to this protocol.

To document habitual physical activity in the control group, participants allocated to the standard of care group will complete the International Physical Activity Questionnaire – Short Form (IPAQ-SF) at baseline, preoperatively and six weeks postoperatively.

Intervention group (pre- and rehabilitation program):

At baseline, patients will receive an information brochure regarding the training program with a description of the exercises and nutritional supplements.

As a part of the training program will be based on the patient's heart rate, patients in the intervention group will receive a watch that is able to measure heart rate. No information (metrics) of the watch will be collected. The heart rate zones will be determined for every patient during the baseline CPET, subsequently training will be personalised.

Prehabilitation Phase (4 weeks-program)

During the prehabilitation phase (before surgery), patients follow a combined physical, mental and nutritional care pathway.

Physical Prehabilitation

Physical prehabilitation consists of condition and strength training. Training is performed at the patient's home combined with in-hospital training:

- **Bicycle-based interval training (T1):** cycling based on interval will be performed at home. The first training will be under supervision (High School students: Vives “opleiding zorgtechnologie”). If deemed necessary according to the supervision, subsequent training can also be performed under supervision. A stationary bike will be delivered to the patient’s home by Goed Zorgwinkel (Tunturi signature F20).
- **In-hospital strength training combined with cycling (heart rate zone 2) (T2):** this training will be under the supervision of healthcare professionals.

Training adherence and perceived exertion will be recorded by the patients using a patient diary and BORG score.

Mental support

Participants randomized to the intervention group will receive a Moonbird device (Moonbird, Antwerpen, Belgium), a handheld breathing guidance device that provides tactile biofeedback to facilitate slow, paced breathing. The device expands and contracts rhythmically, enabling users to synchronize their breathing with the tactile stimulus without requiring visual attention. The intervention is designed to promote relaxation and support psychological well-being by encouraging slow, controlled breathing.

Participants will be instructed to perform one prescribed 10-minute breathing session each day throughout the intervention period. The prescribed session should preferably be completed in the evening before bedtime while sitting comfortably (e.g., in a chair or on a sofa) or lying in bed. Participants will be encouraged to perform the session at approximately the same time each day to promote adherence and establish a consistent relaxation routine.

In addition to the prescribed daily session, participants may use the Moonbird device whenever they experience increased stress, anxiety, or emotional distress, or whenever they feel an additional need for relaxation. Any additional use should also consist of approximately 10-minute sessions. Therefore, the prescribed intervention consists of a minimum of one 10-minute session per day, with additional participant-initiated sessions permitted according to individual needs.

Before commencing the intervention, participants will receive standardized verbal and written instructions on the correct operation and use of the Moonbird device.

Intervention adherence will be assessed using participant-completed study logs. Participants will complete a daily adherence checklist indicating whether the prescribed 10-minute breathing session was performed. The number of additional sessions completed each day will also be recorded.

The Moonbird intervention is intended as an adjunct to standard perioperative care and will not replace any medical, psychological, or supportive care routinely provided during the study period.

Nutritional support

Nutritional support is coordinated at AZ Groeninge and supported by the Food Innovation Park (Roeselare) and includes:

- Nutritional anamnesis by the study coordinator
- Individualized dietary advice, including protein-rich diet recommendations
- To maintain an optimal nutritional status during the pre- and rehabilitation program, all patients will receive a nutritional supplement: Whey Protein Isolate Vanille (Deba Pharma, Kortrijk, Belgium). All ingredients are conform with E.E.C. requirements as defined in regulation (EC) 1333/2008 regarding food additives.
  Recommended usage: Dissolve 30 grams powder in 200 ml milk or beverage of the patient's choice. Mix the this in a shaker/blender.

After the 4 week-program, patients will repeat the Pre/Rehab test.

Postoperative Rehabilitation

After surgery, patients continue rehabilitation primarily at home. Postoperative rehabilitation includes:

- Gradual resumption of physical training (condition and strength exercises)
- Continued breathing exercises (moonbird)
- Intake of nutritional supplements

During the 2 weeks after surgery, patients will be advised to remain active based on their own feeling (no heavy training). Thereafter, patients resume the T1, and T2 training.

Detailed training scheme PREHABILITATION PHASE:

Training schemes T1 and T2 will be used during the prehabilitation phase (between **Visit 1** and **Visit 2**).

Participants allocated in the intervention group will perform a home-based cycling program three times per week (Monday, Wednesday and Saturday) during both the prehabilitation and rehabilitation phases. Training intensity will be individualized based on cardiopulmonary exercise testing (CPET) results and prescribed according to each patient's first ventilatory threshold (VT1) and second ventilatory threshold (VT2). Patients will be supervised by trained students and monitored using heart rate. Cadence (RPM) will be monitored throughout all cycling sessions.

Patients will be instructed to maintain a cadence of 75-90 RPM during continuous endurance training and recovery periods, 85-95 RPM during high-intensity interval training (HIIT) intervals, and 50-60 RPM during torque focused sessions.

To optimize comfort and physiological responses during exercise, patients will be advised to use a fan during training sessions (if possible), avoid training in a fasted state, and maintain adequate hydration throughout exercise.

All aerobic exercise sessions will be prescribed according to the participant's CPET-derived ventilatory thresholds. Heart rate will be continuously monitored using a wearable heart rate monitoring device to ensure participants remain within their prescribed training zones. Exercise adherence, heart rate responses, and training intensity will be monitored throughout the intervention period.

T1 scheme: Bicycle-based interval training at home

	Monday	Wednesday	Saturday	Total cardio
Week 1	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u35
	20min : 1-10 min **70%vt1** 11-20 min **100%vt1**	20min **80%vt1**	25min **100%vt1**	
	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	
Week 2	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	6min warm-up cycling **40%vt1**	1u40
	20min **80%vt1**	25min **100%vt1**	6x1min **vt 2** with 3 min cool down cycling 40**%vt1** between intervals *(=interval/HIIT)*	
	5min cool-down cycling **40%vt1**	6min cool-down cycling **40%vt1**	4min cool-down cycling **40%vt1**	
Week 3	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u45
	25min **100% vt1**	5x1 min 50/60 RPM with 2 min cool down cycling **40%vt1** between intervals *(=Torque/interval)*	30min **80%vt1**	
	5min cool-down cycling **40%vt1**	10 mincool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	
Week 4	5 min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u34
	6x1min **vt 2** with 3 min cool down cycling 40**%vt1** between intervals *(=interval/HIIT)*	20min **100%vt1**	20min **100%vt1**	
	4 min cool down cycling **40%vt1**	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	

Strength training sessions will be performed twice weekly under the supervision of a certified sports physiotherapist in AZ Groeninge. The program combines machine-based resistance training with functional core stability exercises. Machine-based resistance training was performed using the Technogym Selection Line (Basic Module E030BR0), consisting of the following exercises:

- Low Row (latissimus dorsi and biceps brachii)
- Chest Press (pectoralis major and triceps brachii)

- Vertical Traction (latissimus dorsi and biceps brachii)
- Leg Press (quadriceps, gluteal muscles, and triceps surae)
- Leg Curl (hamstrings)
- Leg Extension (quadriceps)

In addition to machine-based resistance training, participants performed functional core stability exercises on exercise mats, including:

- Supported Dead Bug Leg Control
- Supported Dead Bug Arms
- Quadruped Holding
- Sahrmann Heel Taps

The specific exercises, repetitions, and progression are described in the training schedules below.

T2 scheme: In-hospital strength training combined with cycling

	Tuesday	Thursday
Week 1	-Technogym: 3x15 repetitions at 50% 1RM -Core stability: • Supported Dead Bug Leg Control (heel slides) 2x15 • Supported Dead Bug Arms 2x15 • Quadruped Holding 3x10sec	-Technogym: 3x15 repetitions at 50% 1RM -Core stability: • Supported Dead Bug Leg Control (heel slides) 2x15 • Supported Dead Bug Arms 2x15 • Quadruped Holding 3x10sec
Week 2	-Technogym: 3x15 repetitions at 50% 1RM	-Technogym: 3x15 repetitions at 50% 1RM

	-Core stability: • Supported Dead Bug Leg Control (heel slides) 2x20 • Supported Dead Bug Arms 2x20 • Quadruped Holding 3x15sec	-Core stability: • Supported Dead Bug Leg Control (heel slides) 2x20 • Supported Dead Bug Arms 2x20 • Quadruped Holding 3x15sec
Week 3	-Technogym: 4x6 repetitions at 70% 1RM -Core stability: • Supported Dead Bug Leg Control (heel lifts) 2x20 • Supported Dead Bug Arms (+2kg) 2x20 • Quadruped Holding 3x20sec	-Technogym: 3x25 repetitions at 50% 1RM -Core stability: • Supported Dead Bug Leg Control (heel slides) 2x20 • Supported Dead Bug Arms (+2kg) 2x20 • Quadruped Holding 3x20sec
Week 4	-Technogym: 4x6 repetitions at 70% 1RM -Core stability: • Sahrmann Heel Taps 3x10 • Supported Dead Bug Arms (+2kg) 3x15 • Quadruped Holding 3x25sec	-Technogym: 4x6 repetitions at 70% 1RM -Core stability: • Sahrmann Heel taps 3x10 • Supported Dead Bug Arms (+2kg) 3x15 • Quadruped Holding 3x25sec

Before the strength training, patients will cycle at HR zone 2 in the hospital.

All strength training sessions were supervised by a certified sports physiotherapist. Training intensity was individualized based on each patient's one-repetition maximum (1RM), which was assessed prior to initiation of the exercise program. Resistance loads were prescribed as a percentage of the patient's individual 1RM. If patients were unable to complete the prescribed workload, the training load was reduced by 10%.

On Friday and Sunday, patients need to rest.

Detailed training scheme REHABILITATION PHASE:

During the first two weeks after surgery (between **Visit 3** and **Visit 4**), the patients will only perform light exercises based on the patient's possibilities. During this period, the patients will not receive a formal training scheme.

Training schemes T1 and T2 will be used during the rehabilitation phase (between **Visit 4** and **Visit 5**).

T1 scheme: Bicycle-based interval training at home

	Monday	Wednesday	Saturday	Total cardio
Week 1	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u35
	20min : 1-10 min **70%vt1** 11-20 min **100%vt1**	20min **80%vt1**	25min **100%vt1**	
	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	
Week 2	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	6min warm-up cycling **40%vt1**	1u40
	20min **80%vt1**	25min **100%vt1**	6x1min **vt 2** with 3 min cool down cycling 40**%vt1** between intervals *(=interval/HIIT)*	
	5min cool-down cycling **40%vt1**	6min cool-down cycling **40%vt1**	4min cool-down cycling **40%vt1**	

Week 3	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u45
	25min **100% vt1**	5x1 min 50/60 RPM with 2 min cool down cycling **40%vt1** between intervals *(=Torque/interval)*	30min **80%vt1**	
	5min cool-down cycling **40%vt1**	10 mincool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	
Week 4	5 min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	5min warm-up cycling **40%vt1**	1u34
	6x1min **vt 2** with 3 min cool down cycling 40%**vt1** between intervals *(=interval/HIIT)*	20min **100%vt1**	20min **100%vt1**	
	4 min cool down cycling **40%vt1**	5min cool-down cycling **40%vt1**	5min cool-down cycling **40%vt1**	

T2 scheme: In-hospital strength training combined with cycling

	Tuesday	**Thursday**
Week 1	-Technogym: 3x20 repetitions at 50% 1MR -Core stability: • Supported Dead Bug Leg Control (heel slides) 2x20 • Supported Dead Bug Arms 2x20 • Quadruped Holding 3x15sec	-Technogym: 3x20 repetitions at 50% 1RM -Core stability: • Supported Dead Bug Leg Control (heel slides) 2x20 • Supported Dead Bug Arms 2x20 • Quadruped Holding 3x15sec
Week 2	-Technogym: 4x6 repetitions at 70% 1RM -Core stability: • Supported Dead Bug Leg Control (heel lifts) 2x20 • Supported Dead Bug Arms (+2kg) 2x20 • Quadruped Holding 3x20sec	-Technogym: 3x25 repetitions at 50% 1RM -Core stability: • Supported Dead Bug Leg Control (heel lifts) 2x20 • Supported Dead Bug Arms (+2kg) 2x20 • Quadruped Holding 3x20sec
Week 3	-Technogym: 4x6 repetitions at 70% 1RM -Core stability • Sahrmann Heel Taps 3x10 • Supported Dead Bug Arms (+2kg) 3x15 • Quadruped Holding 3x25sec	-Technogym: 4x6 repetitions at 70%1RM -Core stability: • Sahrmann Heel Taps 3x10 • Supported Dead Bug Arms (+2kg) 3x15 • Quadruped Holding 3x25
Week 4	-Technogym: 4x4 repetitions at 80%1RM	-Technogym: 4x4 repetitions at 80%1RM

	-Core stability: • Sahrmann Heel Taps 3x15 • Supported Dead Bug Arms (+2kg) 3x20 • Quadruped Holding 3x30sec	-Core stability: • Sahrmann Heel taps 3x15 • Supported Dead Bug Arms (+2kg) 3x20 • Quadruped Holding 3x30sec

Before the strength training, patients will cycle at HR zone 2 in the hospital.

All strength training sessions were supervised by a certified sports physiotherapist. Training intensity was individualized based on each patient's one-repetition maximum (1RM), which was assessed prior to initiation of the exercise program. Resistance loads were prescribed as a percentage of the patient's individual 1RM. If patients were unable to complete the prescribed workload, the training load was reduced by 10%.

On Friday and Sunday, patients need to rest.

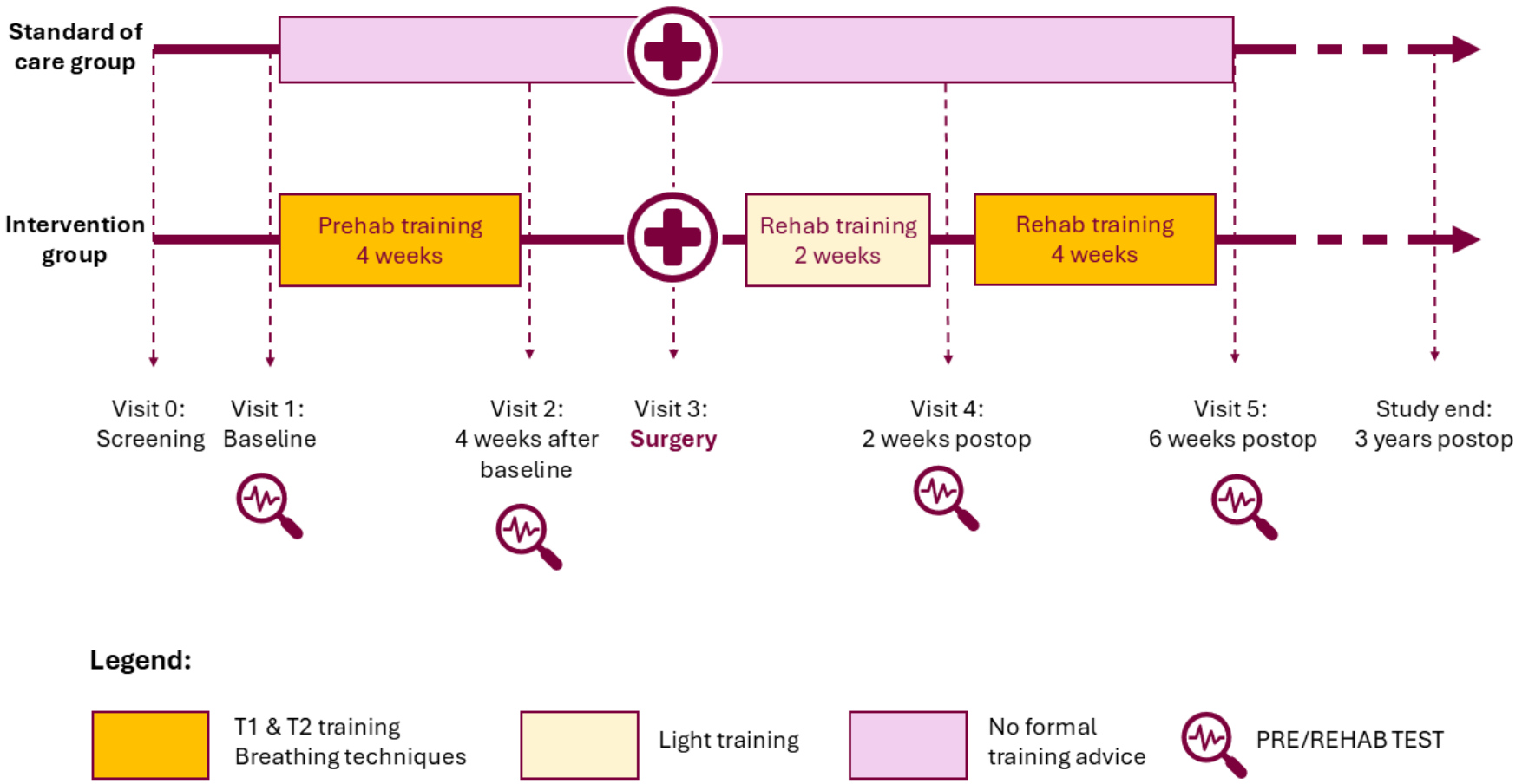


Table 1: Flowchart

	Screening£	Baseline £	Prehabilitation phase	Surgery	Postoperative Rehabilitation phase		Follow-up period
	Visit 0	Visit 1	Visit 2 (4 weeks after baseline)	Visit 3 (max. 5 weeks after baseline)	Visit 4 (2 weeks postop)	Visit 5 (6 weeks postop)	Visit 6 (3 years postop)
IFC	X						
In- and exclusion criteria	X						
Demographic information	X						
Comorbidities	X						
Weight		X	X		X	X	
Length		X					
Blood pressure		X	X		X	X	
Heart rate		X	X		X	X	
Oxygen saturation		X	X		X	X	
Cardiologic consult (ECG, exercise ECG, and echocardiography)	X						
Nutritional intake anamnesis		X					

PG-SGA SF (questionnaire regarding nutritional intake)		X	X		X	X	
Information regarding nutritional supplements∞		X					
Surgery and disease related information		X					
Breathing exercises (moonbird) ∞			X		X	X	
VO2 Max test – CPET		X	X			X	
Pre/rehab Test • Biodex Lower Quadrant • Single leg calf raises • Sit-to-stand test • Hand grip strength • 6 MWT		X	X		X	X	
Dispense watch to measure heart rate during exercises∞		X					

Collect watch∞						X	
Surgery (collect standard of care information)				X			
Blood collection (CRP, WBC, troponin, Ferritin, Albumin)		X	X		X	X	
Blood collection: IL-6, IL-8, IL-10, TNF-α		X	X			X	
EQ5D		X	X		X	X	
EORTC QLQ-C30		X	X		X	X	
IPAQ-SF (control group only)		X	X			X	
Assessment of (S)AEs			X		X	X	
Dispense/Review patient diary (to determine compliance of nutritional intake and training)∞		X	X		X	X	
BORG scale∞			X			X	
Comprehensive complication index					X	X	

Information on hospital readmission					X	X	
Semi-structured interview[∞]						X	
3-year disease-free survival							X
3-year overall survival							X

ICF: Informed consent form, ECG: Electrocardiogram, PG-SGA SF: Patient-generated subjective global assessment, MRI: Magnetic Resonance Imaging, CPET: Cardiopulmonary Exercise Test, 6MWT: 6 Minute Walk Test, CRP: C-reactive Protein, WBC: White Blood Cell Count, IL: Interleukin, TNF-α: Tumour Necrosis Fator alpha, EQ5D: EuroQol 5 Dimensions, EORTC QLQ-C30: EORTC QLG Core Questionnaire, (S)AE: (Serious) Adverse Event, BORG: Borg Rating of Perceived Exertion (RPE) scale

There should be as little time as possible between visits 2 and 3.

[£]*Screening and baseline can take place on the same day*

[∞]*Only the intervention group*

Important: the exercise ECG and CPET cannot be carried out on the same day. Between screening and baseline is a window of 1 week to collect all the necessary parameters.

10.1. Visits

10.1.1. Screening (Visit 0)

- ICF
- Inclusion and exclusion criteria
- Demographic information
- Comorbidities
- Cardiologic consultation (ECG, exercise ECG, echocardiography)

10.1.2. Baseline (Visit 1)

- Body weight
- Length
- Vital signs (Blood pressure, heart rate, oxygen saturation)
- Nutritional intake anamnesis
- PG-SGA SF questionnaire
- Information regarding nutritional supplements (intervention group)
- CPET (VO2Max)
- Pre/Rehab test:
    - Biodex lower quadrant
    - Single leg calf raises
    - Sit-to-stand test
    - Hand grip strength
    - 6MWT
- Dispense watch to measure heart rate (intervention group)
- Blood collection
    - CRP
    - WBC
    - Troponin
    - Ferritin
    - Albumin
    - IL-6
    - IL-8
    - IL-10
    - TNF-α
- EQ5D
- EORTC QLQ-C30
- Surgery and disease related information:
    - Type of surgery (major liver resection or minor liver resection)
    - Surgical approach (open or minimally invasive (laparoscopic or robotic))
    - ASA (American Society of Anesthesiologists Physical Status) score

  - Indication for surgery
  - Redo liver
  - Neoadjuvant chemotherapy
- Dispense patient diary (compliance nutritional intake and training, intervention group)

10.1.3. Four weeks after baseline (Visit 2)

- Weight
- Vital signs (Blood pressure, heart rate, oxygen saturation)
- PG-SGA SF questionnaire
- Breathing exercises (moonbird, intervention group)
- CPET (VO2Max)
- Pre/Rehab test:
  - Biodex lower quadrant
  - Single leg calf raises
  - Sit-to-stand test
  - Hand grip strength
  - 6MWT
- Blood collection
  - CRP
  - WBC
  - Troponin
  - Ferritin
  - Albumin
  - IL-6
  - IL-8
  - IL-10
  - TNF-α
- EQ5D
- EORTC QLQ-C30
- Assessments of (S)AEs
- Review patient diary (compliance, intervention group)

10.1.4. Surgery (Visit 3)

- Information regarding the surgery according to standard of care
  - Blood loss (ml)
  - Operative time (min)
  - Blood transfusion
  - Length of hospital stay
  - Hospital readmission

10.1.5. Two weeks postop (Visit 4)

- Weight
- Vital signs (Blood pressure, heart rate, oxygen saturation)
- PG-SGA SF questionnaire
- Breathing exercises (moonbird, intervention group)
- Pre/Rehab test:
    - Biodex lower quadrant
    - Single leg calf raises
    - Sit-to-stand test
    - Hand grip strength
    - 6MWT
- Blood collection
    - CRP
    - WBC
    - Troponin
    - Ferritin
    - Albumin
- EQ5D
- EORTC QLQ-C30
- Assessments of (S)AEs
- Review patient diary (compliance, intervention group)
- Comprehensive complication index
- Hospital readmission

10.1.6. Six weeks postop (Visit 5)

- Weight
- Vital signs (Blood pressure, heart rate, oxygen saturation)
- PG-SGA SF questionnaire
- Breathing exercises (moonbird, intervention group)
- CPET (VO2Max)
- Pre/Rehab test:
    - Biodex lower quadrant
    - Single leg calf raises
    - Sit-to-stand test
    - Hand grip strength
    - 6MWT
- Blood collection

  - CRP
  - WBC
  - Troponin
  - Ferritin
  - Albumin
  - IL-6
  - IL-8
  - IL-10
  - TNF-α
- EQ5D
- EORTC QLQ-C30
- Assessments of (S)AEs
- Review patient diary (compliance, intervention group)
- Comprehensive complication index
- Collect watch (intervention group)
- Comprehensive complication index
- Hospital readmission
- Semi-structured interview (subpart of the intervention group)

10.1.7. Three years postop (Visit 6)

- 3-year disease-free survival
- 3-year overall survival

10.1.8. During the training phase (intervention group)

- Patients will complete the BORG scale after every training

10.2. Recruitment and informed consent procedure

The investigator will obtain documented consent from each potential subject prior to participation in this study. Consent must be documented by the subject's dated signature on a consent form along with the dated signature of the person conducting the consent discussion. A copy of the signed and dated consent form should be given to the subject before participation in the trial. The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the approval of the Ethics Committee (EC) in advance of use. Specifics about the study and the included population will be included in the consent form.

In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to good clinical practice (GCP) guidelines and to the ethical principles that have their origin in the Declaration of Helsinki.

10.3. Procedures

Cardiologic consult

During the screening, patients will have a cardiologic consult to determine whether they are capable to follow the trial's training program. During this consultation, an ECG, exercise ECG, echocardiography will be obtained. Both patients from the intervention and usual care group will have this consult, as ejection fraction will be used to stratify patients during randomisation.

Demographic information

At screening, demographic data will be collected. This will include birthyear, gender, smoking history (never, past or current) with indication of the number of pack years (1 pack (25 cigarettes) daily for 1 year is 1 pack year), and alcohol intake (yes or no) and numbers of units per week.

Comorbidities

The comorbidities will be collected and recorded for every patient.

In this trial, we will focus on the following comorbidities classification:

- No comorbities
- Arterial hypertension (AHT)
- Chronic obstructive pulmonary disease (COPD)
- Insulin dependent diatbetes mellitus (IDDM)
- Non-Insulin dependent diatbetes mellitus (NIDDM)
- Cardiac-vascular
- Pulmonary
- Vascular
- Endocrine
- Nefrology
- Other oncologic
- Other

Vital signs and BMI

BMI (Length and weight) and vital sings (blood pressure, heart rate, oxygen saturation) will be determined and collected during the trial.

CPET

Both patients in the intervention and usual care group will perform a cardiopulmonary exercise test (cycling) to determine the VO2Max. This test will be carried out at baseline, 4-weeks after baseline, and after 6-weeks postop training in the hospital (az groeninge). This test will be supervised by trained healthcare professionals.

As a part of the training program will be based on the patient's heart rate, these zones will be determined for every patient during the baseline CPET, subsequently training will be personalised.

Pre/Rehab test

- **6 Minute Walk Test**
  The 6MWT assesses an individual's capacity to sustain moderate physical activity. Participants are instructed to walk back and forth for six minutes at a self-selected pace that induces fatigue by the end of the test. Standardized encouragement is provided throughout the walk. Participants may rest if necessary. However, any rest periods are included within the six-minute duration.
- **Biodex lower quadrant**
  The Biodex test is designed to assess how well the patient's knee and muscles surrounding the knee function. The patients will perform the test three times with sufficient rest between each effort, and the best result will be used.
- **Single leg calf raises**
  The single leg calf raise test evaluates the strength and endurance of the calf muscle-tendon unit. The patient stands on one leg on a flat surface or a slight incline with the knee straight and trunk upright. During the test, the patient lifts the heel as high as possible and lowers it back down in a controlled manner, maintaining a 1:1 tempo (one second up, one second down). Minimal hand/finger support may be used for balance. The test continues until the participant can no longer lift the heel fully, maintain the pace, or keep proper form. The test will be performed 3 times with sufficient rest between each effort, and the best result will be used.
- **Hand grip strength**
  Hand grip strength is measured using a hand dynamometer. The test is performed in a standing position with the dominant arm tight against the abdomen and the forearm at a right angle. The patient is instructed to squeeze the handle with maximum force for 3 seconds. The participant will perform the test 3 times with sufficient rest between each effort, and the best will be used.
- **Sit-to-stand test**
  The sit-to-stand test is used in clinical and rehabilitation settings to evaluate leg strength, endurance, balance, and functional mobility. The participant sits on a chair

with arms crossed, feet flat on the floor. The participants stand up and sit down 10 times as quickly as possible without using their hands. Their legs must be fully extended when they stand. The time to perform the 10 repetitions is used. The participants perform the test 3 times with sufficient rest between each effort, and the best result will be used.

Nutritional status

At baseline, a study team member will ask the patients regarding their nutritional intake. Moreover, patients in the intervention group will receive information regarding the intake of nutritional supplements.

The Generated Subjective Global Assessment Short Form (PG-SGA-SF) is a validated questionnaire to assess the nutritional status of a patient. The first four boxed are completed by the patient and the other boxes are to be completed by a healthcare professional. The study coordinator will be trained to able to complete the questionnaire.

Patient-reported outcomes (PROs)

During the trial, patients will complete the EQ5D questionnaire and the EORTC QLQ-C30 questionnaire.

PROs will be collected via a website link (REDCap) on a personal computer/smartphone to minimize the risk of incompleteness and transcription errors. Therefore the email address of the patient will be recorded in the CRF. This email will only be accessible for the study team and stored encrypted so anonymity can be guaranteed. In case patients are not able to work with an electronic device or are not able to connect to the web-application an option will be open to fill out the questionnaires on paper.

BORG RPE scale (rating of perceived exertion scale)

After each exercise session, patients will complete the Borg Rating of Perceived Exertion (RPE) scale to assess their perceived level of effort during the activity. In this trial, the CR10 (scale 0 – 10) will be used.

Dispense and collect watch (Multisport-smartwatch CW500M Decathlon + chest strapANT+ Decathlon)

A watch will be provided to patients for use during the training. The device will be used to monitor heart rate and to ensure that patients exercise within the predefined target heart rate zones during the cycling sessions. At the end of the study period, the device will be returned to the study team. The data collected by the device will not be used for study purposes.

Patient Diary

Patients will complete a paper-based diary to record supplement intake and training activities throughout the study period. The diary will be used to assess adherence to the intervention. In addition, patients will complete the Borg Rating of Perceived Exertion (RPE) scale after each exercise session within the diary. The diary will only be provided to the intervention group.

Breathing exercises

Participants in the intervention group will be instructed to perform daily breathing exercises using the Moonbird device.

Moonbird is a handheld, biofeedback-based breathing device that guides users through paced breathing by providing tactile feedback in the hand. By expanding and contracting, the device helps users regulate their breathing rhythm, promoting slow and controlled breathing patterns. The breathing exercises are intended to support relaxation and improve autonomic regulation.

Participants will be instructed to follow the guided breathing sessions on a daily basis throughout the intervention period.

Surgery

All participants will undergo surgery as part of standard of care. The surgical procedure is not part of the study intervention and will be performed according to local clinical practice and standard guidelines.

Comprehensive complication index

Postoperative complications will be assessed using the Comprehensive Complication Index (CCI). The CCI is a validated scoring system that summarizes all postoperative complications into a single continuous score ranging from 0 (no complications) to 100 (death), based on the Clavien–Dindo classification.

Unlike traditional complication reporting, which typically considers only the most severe complication, the CCI captures the cumulative burden of all complications experienced by a patient. This allows for a more sensitive and comprehensive assessment of postoperative morbidity.

Blood markers

Blood samples will be collected to assess inflammatory, cardiac and protein and muscle reserve markers, including C-reactive protein (CRP), white blood cell count (WBC), Interleukin (IL)-6, IL-8, IL-10, Tumour Necrosis Factor (TNF)-α, Troponin, Ferritin and albumin. Once the test results have been determined, the blood will be destroyed. No biological samples will be stored for future research or additional analyses.

Assessments of (S)AEs

Adverse events (AEs) and serious adverse events (SAEs) will be monitored and recorded throughout the study period. All events will be assessed by the study team and documented in accordance with the study protocol and applicable regulatory requirements.

The severity of each event will be graded, and the relationship to the study intervention will be evaluated by the investigator. SAEs will be reported in accordance with institutional and regulatory guidelines.

3-year disease-free survival

Disease-free survival at three years will be assessed. Disease-free survival is defined as the time from surgery to the first occurrence of disease recurrence. Patients without an event will be censored at the time of last follow-up (3 year).

3-year overall survival

Overall survival at three years will be assessed. Overall survival is defined as the time from surgery to death. Patients without an event will be censored at the time of last follow-up (3 year).

Semi-structured interview

Semi-structured interviews will be carried out with patients included in the intervention group to examine their perceptions and experiences regarding the intervention, with a specific focus on implementation of an exercise program. Furthermore, their perceptions regarding the breathing exercises (moonbird) will be examined. The interviews will be conducted at least after 6 weeks post-surgery.

10.4. Semi-structured interviews

The aim is to gain insight into the patients' perceptions regarding the implementation of a multimodal pre- and rehabilitation program.

Dutch-speaking patients of the intervention group will be invited to participate in a semi-structured interview. After signing an ICF, individual, in depth, face-to-face semi-structured interviews will be carried out using an interview guide (Appendix 8). The interview will start with some exploratory questions, followed by more focused questions concerning the objective. The interview guide will be re-evaluated during intermediate analyses if necessary.

We plan to interview participants until data saturation is achieved, defined as no new information emerging from the last 3 interviews. We estimate that this will be after interviewing approximately 15 participants.

The interviews will be conducted in a quiet and private place at az groeninge, Kortrijk, if feasible, otherwise this will be done online. Interviews will be recorded with an audio recorder and transcribed verbatim. During the interview, field notes can be made regarding body language of the participant or other circumstantial information if deemed necessary by the interviewer.

A thematic analysis will be carried out.

The audio recordings will be digital files and will be stored on a secured place with restricted access, separately from the participant identification list. The recordings will be retained for a period of 5 years after which they will be securely destroyed.
. . Before destroying the audio recordings, a quality check of the transcripts will be performed by an independent person of the research team, who is compliant with the confidentiality rules.

10.5. Withdrawal criteria

10.5.1. Discontinuation of study intervention

If the intervention is stopped early, the reason should be recorded in the participant's medical records and be reported in the CRF whether it is due to either the participant's, legal guardian's or clinician's decision. Reasons for stopping protocol intervention may include, but are not limited to:

- The study participant and/or participant's guardian does not wish to continue with further study intervention
- Occurrence of a medical condition or complication that makes continued participation unsafe
- Clincial deterioration of the participant's general condition
- Newly identified contraindications to participation in the exercise program
- The participant experiences the intervention as excessively burdensome and wishes to stop

The study will be analysed on an intention-to-treat (ITT) basis and all participants who stop randomised study intervention will remain in the study for follow-up unless the participant

and/or legal guardian explicitly withdraws consent for data collection. Additionally, a per-protocol analysis will be conducted.

10.5.2. Withdrawal of consent (discontinuation of study participation)

The participant and/or legal guardian may withdraw consent at any time during the study. For the purposes of this study, withdrawal is defined as:
The participant would like to withdraw consent from the study and is not willing to be followed up for the purposes of the study at any further visits (i.e. only data collected prior to the withdrawal of consent can be used in the study analysis, no data can be collected anymore from this time point).
The details of withdrawal should be clearly documented in the participant's medical records and in the CRF.

10.5.3. Loss to follow-up

If a participant is lost to follow-up, every effort should be made to contact the participant's primary physician (GP) to obtain information on the participant's status. Similarly, if a patient's care is transferred to another clinician, every effort should be made so that follow-up information be obtained.

10.5.4. Arrangements for study participants after their participation in the study ended

No specific arrangements are foreseen for study participants after the end of the study, as the rehabilitation programme is finished at study completion.

10.6. End of study

Patients will be actively followed for approximately 12 weeks (depending on the planning of the cardiologic consultation, surgery, and start of the training scheme), from baseline until 6-weeks post-surgery. After three years, the disease-free survival will be determined. During this 3 years, patients will be followed according to usual care and no additional information will be collected. Study end is 3 years after the baseline visit.

A summary of the study results will be submitted within one year from the end of the study.

11. Safety recording and reporting

11.1. Definitions

Term	Definition

Adverse Event (AE)	Any untoward medical occurrence in a participant who had a medicinal intervention, including occurrences which are not necessarily caused by or related to that intervention.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity • consists of a congenital anomaly or birth defect Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" 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 were more severe.
Unanticipated problems	Any incident, experience, or outcome that meets **all** of the following criteria: 1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; 2. Related or possibly related to participation in the research; 3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

In the INPACT trial, no adverse events have to be recorded in the CRF unless they are categorized as an adverse reaction, related to medical condition under investigation or study intervention.

11.2. Reporting of SAEs

All SAEs occurring from the time of written informed consent until the end of the study intervention (6 weeks postop) must be recorded in the CRF and reported to the Sponsor within 24 hours of the research staff becoming aware of the event.

For each SAEs the following information will be collected:

- full details in medical terms and case description
- event duration (start and end dates, if applicable)
- action taken
- outcome
- seriousness criteria
- causality (i.e. relatedness to study investigation), in the opinion of the investigator
- whether the event would be considered expected or unexpected.

Any change of condition or other follow-up information should be notified to the Sponsor as soon as it is available or at least within 24 hours of the information becoming available. Events will be followed up until the event has resolved or a final outcome has been reached.

Timelines for recording and reporting

The site investigators will report the AEs through the CRF periodically according to the assessment schedule.

11.3. Responsibilities

Principal Investigator (PI):

Checking for AEs when participants attend for follow-up.

1. Using medical judgement in assigning seriousness and causality.
2. Ensuring that all required SAEs are recorded and reported to the Sponsor within 24 hours of becoming aware of the event and provide further follow-up information as soon as available.
3. Ensuring that AEs are recorded and reported to the Sponsor in line with the requirements of the protocol.

Sponsor:

1. Central data collection and verification of AEs, and SAEs according to the study protocol.

11.4. Annual Safety reporting/periodic safety update report

An annual study and safety report will be submitted to the Ethical Committee.

12. Statistical analysis

12.1. Sample size calculation

The endpoint on which the sample size calculation is based upon is the patient's functional capacity presurgery (4 weeks after baseline, Visit 2), measured by the 6-minute walk test, and compared between the intervention and usual care group.

For a superiority design, with a two-sided alpha of 0.05, the null and alternative hypotheses are:

Null hypothesis: A multimodal prehabilitation scheme leads to the same 6MWT-distance compared to usual care, 4 weeks after baseline (presurgery) (there is no difference in 6MWT). H0: $\delta=0$

Alternative hypothesis: A multimodal prehabilitation scheme can be considered as superior to usual care. H1: $\delta\neq0$

Data of the PERIOP-OG trial (Loughney et al. 2024) was used for the sample size calculation. In the PERIOP-OG trial, patients with oesophageal and gastric cancer were randomised to a pre- and post-operative exercise program or standard of care. Their primary endpoint was cardiorespiratory fitness between baseline and pre-surgery using the 6-minute welk test.

These are the parameters taken into account for the sample size calculation, using R 4.6.0 (pwr package):

- Calculation of Superiority / Test for Two means.
- Allocation of 1:1
- Power of 0.80
- Significance level was set at 0.05.
- Control group: mean 6MWT of 506 (SD 140.4) presurgery in the control group of the PERIOP-OG trial (n=24 patients)
- Exercise group: mean 6MWT of 582.1 (SD 108) presurgery in the control group of the PERIOP-OG trial (n=29 patients)

To achieve a power of 80%, 84 patients have to be randomized (n=42 in the intervention group, and n=42 in the standard of care group). We assume a 18% dropout rate until week 4. Therefore, we aim to randomize 103 patients.

12.2. Missing data

Several strategies will be conducted to avoid missing data as much as possible. For instance, all site personnel will be trained on the protocol and it will be checked if all staff members know their responsibilities. However, despite these measures missing data may still arise. In that case, missing data in outcome measures will be handled according to the instrument developers' guidelines. Moreover, we will examine if missing data can be assumed as missing at random.

We will compare dropout between arms. More specifically, the amount of dropout, the time point of dropout, and the reason for dropout will be compared.

12.3. Statistical Analysis plan

12.3.1. Summary of baseline data

The baseline variables will be used to assess comparability of the randomisation arms, and they will be reported as proportions or means with their standard deviations or median and interquartile range, when appropriate.

Variable	Definition	Measurement level
Age		Continuous
BMI (kg/m2) at BL	Body Mass Index	Continuous
Sex		Dichotomous
Smoking status at BL	Status: never, previous, current	Categorical
Alcohol intake at BL	consumption of any form of alcohol, units per week	Ordinal
Comorbidities at screening		Categorical
Ejection fraction		Continuous
CRP (mg/l) at BL	C-reactive protein	Continuous
WBC at BL	White Blood Cell Count	Continuous
Ferritin		Continuous
Albumin		Continuous
IL-6 at BL	Interleukin 6	Continuous
IL-8 at BL	Interleukin 8	Continuous
IL-10 at BL	Interleukin 10	Continuous
TNF-α	Tumour Necrosis Factor alpha	Continuous
Troponin		Continuous
Type of surgery	major liver resection or minor liver resection	Categorical

Surgical approach	open or. minimally invasive (laparoscopic or robotic)	Categorical
ASA score	American Society of Anesthesiologists Physical Status	Categorical
Indication for surgery		Categorical
Redo liver		Categorical
Neoadjuvant chemotherapy		Categorical
VO2Max at BL		Continuous
Biodex lower quadrant at BL		Continuous
Single leg calf raises at BL		Continuous
Sit-to-stand test at BL	Expressed in time	Continuous
Hand grip strength at BL	Expressed in kg	Continuous
6 Minutes walking test at BL	Expressed in meter	Continuous
PG-SGA SF total score at BL		Continuous
EORTC QLQ-C30		Continuous
EQ5D at BL	5 dimensions questionnaire for health-related quality of life	Continuous

BL: Baseline

12.3.2. Primary endpoint

The primary endpoint is to compare the patient's functional capacity presurgery (4 weeks after baseline), measured by the 6-minute walk test, between the intervention and usual care group.

The study will be analysed on an ITT basis. Additionally, a per-protocol analysis will be conducted.

The 6MWT is continuous variable. The distribution of the 6MWT data will be visually checked using histogram and formally tested for normality using the Shapiro-Wilk test. Data will be presented as mean and standard variation for normally distributed variables, or as median and interquartile range (IQR) for non-normally distributed variables. Statistical analysis will be performed usingappropriate parametric or non-parametric tests depending on the distribution of the data. Parametric tests will be used for normally dstributed data.. If the assumption of normality is not met,, non-parametric tests will be applied. If appropriate, t-tests or Mann-Whitney U tests will be carried out.

12.3.3. Secondary endpoint

Secondary endpoints are:

- *Change in distance (cm) on the 6MWT from baseline until V2, and from baseline until V5. Compare the hand grip strength, Vo2max, Biodex lower quadrant, Single leg calf raises, sit-to-stand test, 6MWT at the different timepoints between the two groups*
- *PROMs for HRQoL (EORTC QLG Core Questionnaire (EORTC QLQ-C30), EQ5D)*
- *Comprehensive Complication Index Score (CCI)*
- *Length of hospital stay*
- *Nutritional status measured by the PG SGA SF and compliance of nutritional supplements intake*
- *Safety: total number of AEs and SAEs, and proportion of patients with a(n) (S)AE*
- *Study compliance: a BORG scale will be completed by patients. Patients will complete an exercise diary to measure the training compliance.*

Secondary outcomes will be described as means and standard deviation, or median and interquartile range where data are continuous and normally or not-normally distributed, respectively. Categorical variables will be described as numbers and proportions.
Statistical methods will include t-tests and Mann-Whitney U tests for continuous normally or not-normally distributed variables at a single time-point, respectively. Categorical outcomes will be analysed using a Chi-square test for a single time point.
Longitudinal data will be analysed by appropriated longitudinal analysis techniques (Generalized Estimating Equation, Generalized Linear Model).

Proportion of patients who achieve a 3-year disease-free survival and a 3-year overall survival, compared between the two groups

Kaplan–Meier survival analyses and log-rank tests will be carried out. Cox proportional hazards models will be used to identify factors associated with disease-free survival and overall survival.

Patients' perceptions will be determined on the implementation of the training program (semi-structured interviews).

A thematic analysis will performed based on the principles of grounded theory and the constant comparative method. After transcribing the interviews verbatim, the researchers will familiarized themselves with the data. The transcripts will be coded line-by-line, creating initial codes, which

are labels, words or small sentences of a transcript's fragment. Afterwards, similar codes will be grouped into subthemes and themes.

12.3.4. Other statistical considerations

Exploratory outcomes are:

Exploratory health economic analysis

An exploratory health economic analysis will be carried out. The EQ-5D-5L data will be used to estimate quality-adjusted life years using time-weighted utility scores. The utility value set of Belgium, published by the KCE, will be used (An EQ-5D-5L value set for Belgium). The area under the curve denotes the QALY.

Laboratory outcomes: CRP, WBC, IL-6, IL-8, IL-10, TNF-α, troponin, Ferritin, Albumin

Laboratory outcomes are considered exploratory outcomes. As the study is not powered to detect statistically significant differences in these parameters, the analyses will be primarily descriptive.
Data will be presented using appropriate descriptive statistics and 95% confidence intervals where applicable.
No data-driven hypothesis testing will be performed as part of the primary analysis. Any additional analyses of laboratory outcomes will be considered exploratory post-hoc analyses and will be clearly identified as such in any reporting of the study results.

Patients' perceptions will be determined on the effect of the breathing exercises (semi-structured interviews)

A thematic analysis will performed based on the principles of grounded theory and the constant comparative method. After transcribing the interviews verbatim, the researchers will familiarized themselves with the data. The transcripts will be coded line-by-line, creating initial codes, which are labels, words or small sentences of a transcript's fragment. Afterwards, similar codes will be grouped into subthemes and themes.

13. Data handling and management

13.1. Data collection tools and source document identification

Source data will be collected and recorded in the study participants' medical records. They will be kept on a secured location at all times. The collection and processing of source data (from subjects enrolled in this study) will be limited to those data that are necessary to fulfil the objectives of the study. These data will be collected and processed with adequate precautions to ensure confidentiality and compliance with applicable data privacy protection laws and regulations. Appropriate technical and organizational measures to protect the data against unauthorized disclosures or access, accidental or unlawful destruction, or accidental loss or alteration will be put in place. Personnel whose responsibilities require access to personal data agree to keep the data confidential.

Documentation of source data is necessary for the evaluation and validation of clinical findings, observations and other activities during a clinical study. Source documentation serves to substantiate the integrity of study data, confirms observations that are recorded and confirms the existence of study participants. Furthermore source documentation will be available for the following to confirm data collected in the e-CRF: subject identification, eligibility, and study identification; study discussion and date of informed consent; dates of visits; results of safety and efficacy parameters as required by the protocol; record of relevant adverse events and follow-up of adverse events as required by the protocol; administration of medication as prescribed for the study and relevant concomitant medication will be documented in the source data; and date of study completion and reason for early discontinuation of study drug or withdrawal from the study, if applicable. Data collection is the responsibility of the clinical study staff at the site under the supervision of the investigator. The investigator will maintain complete and accurate documentation for the study. All source documents will be reviewed by the clinical team to ensure that they are accurate and complete.

As defined in section 1.52 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guideline for Good Clinical Practice (ICH E6) source documents may include: original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes).

13.2. Case report forms

The study data will be transcribed on a regular basis by study personnel from the source documents onto an CRF (REDCap) in a pseudonymized manner.

Worksheets may be used for the capture of some data to facilitate completion of the e-CRF. Any such worksheets (including but not limited to copies of the e-CRF) will become part of the study participant's source documentation. Data related to the study must be recorded in the e-CRF. Data must be entered into e-CRF in English. Designated site personnel must complete the e-CRF as soon as possible after a subject visit.

The investigator will ensure that data are recorded in the e-CRF as specified in the study protocol and in accordance with the instructions provided.

All e-CRF entries, corrections, and alterations must be made by the investigator or other authorized study-site personnel. Proper audit trails are available to demonstrate the validity of the study data. A copy of the completed e-CRFs will be archived at the study site.

For this study, REDCap will be used as CRF.

Data that are recorded in a structured format in the electronic patient record (KWS) can be extracted from this record. These data does not need to be entered into the CRF. Immediately extracting data from the medical records is expected to reduce the risk of data entry errors.

13.3. Data handling and record keeping

Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679. The investigator will maintain a certified copy of CRFs (REDCap) and all source documents that support the data collected from each study participant, as well as all study documents as specified in ICH/Good Clinical Practice (GCP) Section 8, Essential Documents for the Conduct of a Clinical Trial, and all study documents as specified by the applicable regulatory requirement(s). The investigator will take measures to prevent accidental or premature destruction of these documents.

14. Assessment of risks and safety

14.1. Risks

1. **Exercise-related risks**

Participants allocated to the intervention group will take part in a prehabilitation and rehabilitation programme consisting of cycling, strength training, and breathing exercises. Physical exercise may cause temporary fatigue, muscle soreness, dizziness, shortness of breath, musculoskeletal complaints, or, in rare cases, cardiovascular symptoms. To minimise these risks, all participants will undergo a cardiologic assessment before enrolment, and exercise intensity will be individualized based on the results of the cardiopulmonary exercise test (CPET). Participants with medical conditions that place them at unacceptable risk will be excluded from participation.

2. **Risks related to study assessments**

The study includes physical performance tests (CPET, 6-minute walk test, strength assessments) and blood sampling. These procedures may be associated with temporary discomfort, fatigue, dizziness, pain, bruising, or minor bleeding at the puncture site. All assessments will be performed by trained healthcare professionals according to standard procedures.

3. **Nutritional supplement-related risks**

Participants in the intervention group will receive a whey protein supplement. Although the product is commercially available and generally considered safe, some participants may experience gastrointestinal discomfort, bloating, nausea, or intolerance. Participants will receive appropriate instructions regarding supplement intake and any complaints will be monitored throughout the study.

4. **Device-related risks**

Participants in the intervention group will use a heart rate watch and the Moonbird breathing device. These devices are non-invasive and associated with minimal risk. Potential inconveniences include mild discomfort, difficulties using the devices, or temporary frustration related to their use. Data collected by the watch will not be used for study purposes.

5. **Data privacy risks**

The study involves collection of clinical data and questionnaires. Although all study data will be pseudonymised and stored in secure electronic systems with restricted access, there remains a minimal risk of unauthorised access or data breaches. Appropriate technical and organisational safeguards will be implemented to minimise this risk.

6. **Participant burden**

Participation requires attendance at study visits, completion of questionnaires and diaries, and, for participants in the intervention group, adherence to the training programme. This may result in additional time commitment and inconvenience compared to standard care.

14.2. Benefits

1. **Potential reduction in postoperative complications and improvement in functional recovery**

Previous research suggests that multimodal prehabilitation programmes may reduce postoperative complications, improve functional capacity, and shorten recovery after major oncological surgery. This study aims to evaluate these potential benefits in patients undergoing liver surgery.

2. **Improved understanding of perioperative care**

The study will provide valuable information regarding the effects of a combined exercise, nutritional, and breathing intervention on physical performance, quality of life, nutritional status, and safety in patients undergoing oncological surgery.

3. **Contribution to clinical practice**

The results may support the implementation of evidence-based prehabilitation and rehabilitation programmes within routine cancer care. Such programmes may improve postoperative recovery and contribute to better long-term patient outcomes in the future.

Conclusion

The risks associated with participation in the INPACT study are considered low and primarily consist of temporary discomfort related to exercise, physical testing, blood sampling, and study participation. Appropriate safety measures, including cardiologic screening, supervised training, trained study personnel, and secure data management procedures, will be implemented to minimise these risks. Given the potential benefits for participants and the expected contribution

to improving perioperative cancer care, the anticipated benefits outweigh the foreseeable risks associated with study participation.

15. Study monitoring, audit and inspection

Based on the study-specific risk assessment, the INPACT trial is considered a low-risk study. The study does not involve an Investigational Medicinal Product (IMP) or an investigational medical device, and all study procedures are either part of standard care or associated with a low level of additional risk. Therefore, no routine study monitoring visits will be foreseen.

The investigator will permit study-related audits, ethics committee (EC) review and regulatory inspection, providing direct access to all related source data / documents.

CRF's and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by auditor and inspection by health authorities. The accuracy of the data will be verified by review of the source documents.

16. Archiving of documentation

The Sponsor is responsible for archiving study specific documentation (such as but not limited to protocol, potential amendments, final report and database) according to ICH-GCP. Source data and site-specific study documents (such as, but not limited to, informed consent form (ICF)) will be archived locally on site according to local practice and guidelines for at least 20 years. Archived data may be held on electronic record, provided that a backup exists and that hard copies can be obtained, if required. Destruction of essential documents will require authorization from the Sponsor.

17. Ethical and regulatory considerations

17.1. Regulatory authorities review and reports

The study will be conducted in compliance with the principles of the Declaration of Helsinki (current version), the principles of GCP and in accordance with all applicable regulatory requirements. Before the start of the study, this protocol, the informed consent forms and other related documents, will be submitted for review to the Ethics Committee (EC). The study shall not commence until approval have been obtained.

Any subsequent protocol amendments will be submitted to the EC for approval. No substantial amendments that require review by EC will be implemented until the EC grants a favourable opinion for the study.

The study can and will be conducted only on the basis of prior informed consent by the study participants to participate in the study. Extensive discussion of risks and possible benefits of participation will be provided to the patients. A signed ICF will be obtained for all study

participants prior to their enrolment and participation in the study in compliance with all applicable laws, regulations and the approval of the Ethics Committee. The site shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

All correspondence with the EC shall be retained in the Investigator Site File.

The Principal Investigator acknowledges that it is his responsibility to produce annual progress reports, and he will do so by submitting to the EC within 30 days of the anniversary date on which the favourable opinion was given, and annually until the study is declared ended.

The Principal Investigator shall notify the EC of the end of the Study. Should the study be ended prematurely, the Principal Investigator will notify the EC and include the reasons for the premature termination. The Principal Investigator will submit a final report with the results, including any publications/abstracts (if applicable), to the EC.

17.2. Public and Patient Involvement

The public and patients were not involved in the designing of this study.

17.3. Insurance

In accordance with the Belgian Law relating to experiments on human persons dated 07 MAY 2004, the sponsor will assume, even without fault, the responsibility of any damages incurred by a participant and linked directly or indirectly to the participation to the study and will provide compensation for the damages. The sponsor will therefore take out a no-fault insurance. Before the start of the trial, approval regarding the insurance taken out by the sponsor will be sought from the EC.

18. Regulatory compliance

Before the start of the study, this protocol and other related documents will be submitted for review to the EC. The study shall not commence until an approval is obtained from the regulatory authorities.

This study protocol and the conduct of the study in general is in compliance with applicable law, including but not limited to with the Belgian law of May 7th 2004, regarding experiments on the human person and any relevant amendments.

18.1. Protocol compliance

The Principal Investigator is responsible for ensuring that the clinical study is performed in accordance with the protocol, current ICH guidelines on GCP, and applicable regulatory and

country-specific requirements. GCP is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. 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 Declaration of Helsinki, and that the clinical study data are credible.

It is acknowledged and agreed that prospective, planned deviations or waivers to the protocol are not allowed under applicable regulations on clinical studies and must not be used. However, should there be an accidental protocol deviation, such deviation shall be adequately documented on the source documents and on the relevant forms and reported to the Principal Investigator and Sponsor immediately. Protocol deviations that are found to frequently recur will require immediate action. The Principal Investigator acknowledges that such recurring protocol breaches could be potentially classified as a serious violation.

18.2. Notification of Serious Breaches to Regulation, and/or the protocol

A “serious breach” is a breach of the protocol which is likely to effect to a significant degree:

- the safety or physical or mental integrity or right of the participants of the study; or
- the scientific value of the study (reliability and robustness of the data generated in the study)

The sponsor will be notified immediately of any case where the above definition applies during the study conduct phase. The sponsor of a study will notify the regulatory authority in writing of any serious breach of the conditions and principles of GCP in connection with that study; or the protocol relating to that study, as amended from time to time, within 7 days of becoming aware of that breach.

18.3. Data protection and patient confidentiality

The study will be conducted in compliance with the requirements of the current version of the Belgian Act on the protection of privacy in relation to the processing of personal data and the European Data Protection Act. Any collection, processing and disclosure of personal data, such as patient health and medical information is subject to compliance with the aforementioned personal data protection laws.
Any personal data shall be treated as confidential at all times including during collection, handling and use, and that 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 data protection legislation. The Sponsor shall take appropriate measures to ensure the security of all personal data and guard against unauthorized access to or disclosure of or loss or destruction while in its custody.

The personal data of study participants will be encoded, which means that they can only be related to an identifiable person by means of a unique code. The unique code will only be in the possession of the members of the study team who are in direct contact with the study participants. In no event will the coded personal data include personal identifiers, including any Study participant’s initials. Such coded personal data can only be traced or linked back by said

study team members and said study team members shall treat these codes as strictly confidential.
All study related data and documents will be stored for 20 years, in accordance with Belgian legislation.

19. Dissemination policy

The results of the study shall be disseminated as soon as possible, by disclosing them to the public by appropriate means, including in scientific publications (in any medium, including a peer-reviewed journal).

20. Protocol versions log

Version	Date	Author(s)	Comments
1.0	20/4/2026	Delphine Bertrand, Caroline de Beukelaar, Mathieu D'Hondt, Celine De Meyere	

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22. Appendices

Appendix 1: Main Informed Consent Form INPACT Trial

Appendix 2: Information brochure (2a: Dutch version, 2b: French version)

Appendix 3: Patient diary (V1.0) (3a: Dutch version, 3b: French version)

Appendix 4: EQ5D (4a: Dutch version, 4b: French version)

Appendix 5: PG-SGA SF questionnaire

Appendix 6: EORTC QLQ-C30 (6a: Dutch version, 6b: French version)

Appendix 7: ICF for qualitative substudy with patients

Appendix 8: Interview guide for patients (only Dutch speaking patients, V1.0)

Appendix 9: Patient information brochure