RESEARCH PROTOCOL

Cancer Rehabilitation for hepato-pancreato-biliary cancer patients undergoing Surgical Treatment (CREST study)

PROTOCOL TITLE 'Cancer rehabilitation for Hepato-Pancreato-Biliary cancer patients undergoing surgical treatment'

DUTCH PROTOCOL TITLE 'Kanker rehabilitatie voor resectabele Hepato-Pancreato-Biliaire kanker patiënten'

Protocol ID	
Short title	CREST study
EudraCT number	
Version	1.5
Date	31-05-21018
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinfomatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: In gastrointestinal cancer patients, overall almost 30% of patients experience severe fatigue while in HPB cancer the vast majority suffers from fatigue. Generally, even after successful cancer treatment, 19 to 38% of disease-free cancer survivors remain fatigue, which underlines its persistent character. The cancer itself, as well as the sequelae after surgical interventions or chemotherapy may lead to physical and psychosocial impairment in cancer patients. As patients experience increased fear and a lower exercise tolerance due to persistent fatigue they are at great risk of spiralling down a vicious circle which progressively enhances these symptoms and further impairs their quality of life and self-management capacity. In patients who have been treated for cancer, psychotherapy and physical exercise are shown to reduce fatigue complaints.

Objective: Since multiple dimensions (physical, emotional and cognitive) seem to be involved in the pathophysiology of fatigue, multidimensional approach to alleviate will probably have a synergistic effect. Previous studies supporting this assumption included general cancer populations or breast and colon cancer patients, who are known for their relatively good prognosis and post-treatment functional outcome.
The purpose of our study is to investigate whether a postoperative rehabilitation program (solution focused psycho- and physical exercise therapy) improves fatigue (primary outcome) and quality of life, muscle mass, and physical fitness (secondary outcomes) in cancer patients operated for HPB malignancies, known to have a more dismal prognosis.

Study design: In this multicentre randomized controlled trial, patients will randomly be assigned to the treatment (rehabilitation program) or control (usual care) group in the four participating centres. After hospital discharge, the treatment group will undergo a supervised, tailored exercise program aimed at both cardiorespiratory fitness (aerobic training) and muscle strength (resistance training) twice a week during twelve weeks. Furthermore, one hour solution focused therapy is offered every other week. The primary outcome will be MFI-General Fatigue, at 12 months after surgery. Secondary outcomes are quality of life, cardiopulmonary fitness, skeletal muscle mass and strength, distribution and intensity of physical activity, MFI-Physical Fatigue, MFI-Mental Fatigue, MFI-reduced activity and motivation, frailty, anxiety, depression, and body weight, and risk of malnutrition assessed preoperatively, at the start and end of the rehabilitation program and six and twelve months after surgery. Validated tests are used to assess these parameters. Furthermore, an effect of the intervention on overall survival will be investigated.

Study population: Adult HPB cancer patients undergoing surgical cancer resection in Erasmus MC (Rotterdam), AMC (Amsterdam), LUMC (Leiden), and UMCG (Groningen) will be included in this study.

Intervention (if applicable): rehabilitation program consisting of physical exercise therapy, psychotherapy and dietary consultation.

Main study parameters/endpoints: General fatigue, assessed with the Multidimensional Fatigue Inventory (MFI).

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: None.

INTRODUCTION AND RATIONALE

Cancer treatment has improved considerably in recent years. One-year overall survival rates of breast and colon cancer patients are as high as 97% and 80% respectively (1). However, these advances have not yet been achieved for all malignancies. For hepatopancreatobiliary (HPB) cancers, surgical resection is often considered the only curative treatment which is only feasible in up to 25% of patients. The one-year overall survival rates of primary hepatic and pancreatic cancer patients in the Netherlands remain as low as 39% and 24% respectively (1). The dismal disease and treatment outcome is not solely affected by tumour characteristics. Additional factors, such as frailty, limit survival in cancer patients (2). Frailty is a state of increased vulnerability of an individual towards stressors, leading to an increased risk of developing adverse health outcomes (3). A hallmark sign of frailty is fatigue, which is the most frequently reported symptom in cancer patients, both during and after cancer treatment (4, 5). In gastrointestinal cancer patients, almost 30% of patients experience severe fatigue (6). Low physical activity is independently associated with severe fatigue before cancer treatment (6). During cancer treatment, rates of fatigue in various patient populations vary between 25 and 99% (7). After successful cancer treatment, 19 to 38% of disease-free cancer survivors remain fatigued, which underlines its persistent character (7, 8). In our own daily practice, we experience that fatigue in the first months is reported very frequently, particularly after major abdominal surgery for HPB cancer. Although the exact pathogenesis of fatigue remains to be revealed, disturbances in physiology, biochemistry and psychology are considered to contribute to this multifactorial symptom (9). Another key determinant of fatigue may be attributed to frailty, an age- and disease related skeletal muscle depletion (i.e. sarcopenia) (10). The prevalence of sarcopenia is common in HPB cancer patients, exceeding rates of 50% in our population (11). These patients experience muscle weakness that leads to physical impairment, increased fatigue and decreased quality of life (5). Furthermore, such sarcopenic and frail patients are more prone to a reduced therapy effect, complications of treatment and increased chemotherapy toxicity (12).

Although preoperative care (e.g. nutritional support and dietary consultation) and perioperative care (i.e. Enhanced Recovery After Surgery [ERAS]) have greatly improved short-term outcomes in surgical HPB cancer patients, the cancer itself, as well as the sequelae after surgical interventions or chemo(radiation)therapy may lead to physical and psychosocial impairment in cancer patients (13). As patients experience increased disease-related fatigue, fear or anxiety and depression, loss of muscle mass and strength, and subsequently a lower exercise tolerance, they are at great risk of spiralling down a vicious circle which progressively enhances these symptoms and further impairs their quality of life and self-management capacity (14, 15). These symptoms particularly occur in the early

postoperative phase. Although this series of events is well recognized as a potential course after major HPB surgery, monitoring of these patients' well-being after treatment frequently remains a neglected, unstandardized aspect of care. And if complaints of fatigue and weakness are recognized, it is still unknown to date how to offer these particular patients the best supportive care.

Since multiple dimensions (physical, emotional and cognitive) seem to be involved in fatigue, a multidimensional approach should be opted for (16). In patients who have been treated for cancer, psychotherapy was shown to significantly reduce fatigue (7). Particularly interventions with a more general approach, aiming at psychological distress, mood and physical symptoms, are effective in reducing fatigue (17) Furthermore, physical exercise has been demonstrated to reduce fatigue in cancer patients (18, 19) and cancer survivors (20, 21). The authors of a recent Cochrane review performed a meta-analysis compromising 56 studies (4068 participants with various cancers) that showed that physical exercise therapy can be regarded as beneficial for patients with cancer-related fatigue during the post-cancer therapy, particularly in patients with solid tumours (18).

A previous study of Van Weert et al. (22) compared the effect of combined physical training and cognitive-behavioural therapy with physical training only and no intervention on cancer-related fatigue in cancer survivors (63.2% breast cancer, 19.7% haematological cancer, 7.9% gynaecological cancer, and 9.2% other cancer). Physical training combined with cognitive-behavioural therapy and physical training alone had significant beneficial effects on fatigue compared with no intervention. Physical training was as effective as physical training with cognitive-behavioural therapy. The study population was not specified and likely included colorectal and breast cancer patients with relatively good prognosis. Furthermore, the physical exercise therapy program in this study included some elements of coping with fatigue, goal setting and exercise-relaxation balance activities, which may have reduced the effect of the cognitive-behavioural therapy. Solution focused therapy has also been proven effective in various patient populations. A great advantage of solution focused therapy is that a fewer number of sessions is needed to be effective compared with cognitive-behavioural therapy (23, 24). This translates in lower costs and could possibly lead to greater patient adherence.

Previous studies have been conducted in cancer patients with a relatively good prognosis, such as breast and colorectal cancer (20-22, 25-32). These populations generally reach a functional status after treatment that is comparable with pre-disease levels and patients may return to regular societal participation. Therefore, the results of these studies may not apply

to patients undergoing surgical resection of malignancies with a more dismal outcome and high morbidity even mortality in the first years after surgery, such as HPB cancer patients. In addition, HPB cancer patients experience a greatly impaired quality of life according to data from the European Organisation for Research and Treatment of Cancer (EORTC) (33). The mean global health status or quality of life in HPB cancer patients (all stages) on the EORTC Quality of Life Questionaire-C30 is 56 points on a scale of 0-100, which is amongst the lowest scores for cancer patients. For example, breast cancer patients, colorectal cancer patients and the general population score 62, 61 and 71.2 respectively (33). Researchers in-(34) and outside (35-37) of our research group have demonstrated that quality of life is greatly impaired in HPB cancer patients, including candidates for surgery. In particular in patients with worsened survival the quality of life is lowest (35). Therefore, we aim to reduce fatigue complaints and increase quality of life in the early palliative phase of patients operated on for HPB malignancies.

1. OBJECTIVES

Primary objective

- To estimate the efficacy of cancer rehabilitation for patients with resectable hepatopancreatbiliary cancer to reduce general fatigue 12 months after discharge as measured by the MFI questionnaire.

Secondary objectives

- To assess the impact of rehabilitation on quality of life (EORTC-QOL C30), Frailty (GFI) and anxiety and depression (HADS).
- To describe the development of MFI-General Fatigue, MFI-Physical Fatigue, MFI-Mental Fatigue, MFI-Reduced Motivation and MFI-Reduced Activity measured preoperatively, at the start and end of the rehabilitation program and six and twelve months after surgery.
- To document the physical status of the patient by measuring the 6 minute walk test, grip and quadriceps strength, muscle mass (L3 muscle index), visceral adipose tissue and malnutrition risk (PG-SGA SF)..
- To describe the general performance of patients using the Karnofsky score, the sit-up and go test and accelerometer activity level measurements.
- To assess patients overall survival at 1, 3, and 5-years after surgery.
- To estimate the cost-utility of the rehabilitation program using QALYs (EQ-5D-5L, QLQ-C30), direct and indirect costs.

2. STUDY DESIGN

This study is a clinical, multi-centre randomized controlled trial.

2.1 Population (base)

All consecutive patients undergoing surgery for HPB malignancies (i.e. bile duct cancer, pancreatic cancer, hepatic cancer) in Erasmus MC (Rotterdam), AMC (Amsterdam), LUMC (Leiden), and UMCG (Groningen) will be considered for eligibility for study participation. Particularly these patients may benefit from the described intervention. After all, they have a dismal prognosis, but are considered fit enough to undergo surgery as this is the only hope for curation.

Approximately 120 HCC, 150 pancreatic cancer and 30 bile duct cancer patients undergo surgery in the four participating centres. Consequently, patient inclusion should be finished within something more than one year with an inclusion rate of 50%. Follow-up will be conducted for 5 years or until death to explore a possible association between the intervention and survival benefit.

2.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Undergoing curative intent surgery for HPB malignancies. Liver surgery will be defined as major if a left or right (extended) hemihepatectomy or if 3 or more segments are resected and minor if less than 3 segments are resected.
- Clinically suspect or histologically confirmed liver, bile duct or pancreatic carcinoma;
- Life expectancy of at least six (6) months;
- Resection performed
- Fatigue score ≥ 4 on a numeric rating scale (NRS) with scores of 0 to 10
- Able to read and understand the Dutch language;
- Written informed consent.

2.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Bone metastases or other high risk of fractures;
- Not able to perform basic activities of daily living (ECOG ≥3);

- Decompensated heart disease, uncontrolled hypertension (systolic blood pressure > 200 mmHg or diastolic blood pressure > 110 mmHg), heart failure (NYHA Class II or greater) or chronic obstructive pulmonary disease causing fatigue;
- Living in nursing homes;
- Cognitive impairment;
- BMI <15 kg^2/m^2, >5% weight loss per month or other health problems that would not allow physical exercise training;
- Anxiety or depression requiring psychiatric consultation;
- Cancer treatment in the previous 5 years (except basal skin cancer);
- Participation in other studies containing elements of physical exercise or psychological therapy.

2.4 Sample size calculation

MFI-General fatigue is the primary outcome of the study. To detect a medium difference in MFI-General fatigue (Cohen's d = 0.50) with a power of 0.80 and alpha of 0.05 (two sided), both groups should consist of 64 patients. With an expected 20% drop out rate (25), a total of 154 patients are needed.

3. TREATMENT OF SUBJECTS

3.1 Investigational treatment

The rehabilitation program consists of physical exercise therapy, psychotherapy and dietary consultation.

3.2 Use of co-intervention

There are no restrictions for participants.

4. INVESTIGATIONAL PRODUCT

4.1 Name and description of investigational product(s)

Not applicable.

4.2 Summary of findings from non-clinical studies

Not applicable.

4.3 Summary of findings from clinical studies

Not applicable.

4.4 Summary of known and potential risks and benefits

Not applicable.

4.5 Description and justification of route of administration and dosage

Not applicable.

4.6 Dosages, dosage modifications and method of administration

Not applicable.

4.7 Preparation and labelling of Investigational Medicinal Product

Not applicable.

4.8 Drug accountability

Not applicable.

5. NON-INVESTIGATIONAL PRODUCT

5.1 Name and description of non-investigational product(s)

Not applicable.

5.2 Summary of findings from non-clinical studies

Not applicable.

5.3 Summary of findings from clinical studies

Not applicable.

5.4 Summary of known and potential risks and benefits

Not applicable.

5.5 Description and justification of route of administration and dosage

Not applicable.

5.6 Dosages, dosage modifications and method of administration

Not applicable.

5.7 Preparation and labelling of Non Investigational Medicinal Product

Not applicable.

5.8 Drug accountability

Not applicable.

6. METHODS

6.1 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

MFI-General Fatigue assessed 12 months after surgery will be used as the primary outcome. Symptoms of fatigue are assessed using the Multidimensional Fatigue Inventory (MFI) (16). This 20-item questionnaire includes the following five scales: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. One can score each question with 1 to 5 points, with sub scores for the five dimensions ranging from 4 to 20. Higher scores indicate increased fatigue.

6.1.2 Secondary study parameters/endpoints

Secondary outcomes are fatigue, frailty, anxiety, depression, quality of life, amount of visceral adipose tissue, skeletal muscle mass and strength, performance status, malnutrition risk and body mass index (BMI) which will be assessed preoperatively, at start and end of the rehabilitation program, and 6 and 12 months after surgery. Furthermore, overall survival will be assessed.

Frailty and anxiety and depression assessment

Frailty will be assessed using the Groningen Frailty Indicator (GFI) (38). The GFI has been developed as a simple screening instrument for frailty. It screens on physical, cognitive, social, and emotional items. The maximum score is 15 points. Patients scoring 5 or more points are considered frail. Anxiety and depression mood will be measured using the Hospital Anxiety and Depression Scale (HADS), consisting of the anxiety (HADS-A) and depression (HADS-D) subscales. Both subscales have a score ranging from 0 to 21 with higher scores indicating more anxiety and depression (39).

Quality of life

The (health-related) quality of life will be assessed using the EORTC-Quality of Life-C30 questionnaire (version 3). The Dutch version of this questionnaire is validated (40).

Body composition measurements

All patients will undergo computed tomography (CT) examinations preoperatively (within 4 weeks preoperative), at baseline (2 weeks after discharge), 17 weeks after discharge and 3, 6 and 12 months hereafter. All examinations are part of standard care and financially covered by the patients' healthcare insurance. The cross-sectional skeletal muscle area (cm^2) will be measured on the level of the third lumbar vertebra (L3). This area will be adjusted for patients' height, resulting in the L3 muscle index (cm^2/m^2). This measure is strongly correlated with total body skeletal muscle mass and this measure is known for its highly reliability and great reproducibility (11, 41). Finally, the amount of visceral adipose tissue will be measured (42). Researchers assessing these two measures will be blinded with regard to whether the patient was part of the treatment group.

Nutritional risk

To assess the nutritional status and the risk of malnutrition all patients are asked to fill in the Patient-Generated Subjective Global Assesment Short Form (PG-SGA SF) (43).

Muscle strength

Muscle strength is a predictor for survival in patients of average and higher age. Furthermore, muscle strength of the extremities are important characteristics of functional performance in elderly (44). Muscle weakness results in decreased self-management and a higher rate of dependency. The strength of the quadriceps muscle will be measured using a handheld dynamometer (MicroFET2). The peak force during contraction will be measured for 5 consecutive seconds (44). A JAMAR® hand dynamometer will be used to measure muscle strength of the upper extremities (45); sitting on a chair with the shoulders adducted and neutrally rotated, the arm in vertical (next to the body) position and the wrist in neutral position, the subject is instructed to squeeze the grip with maximum strength. Decreased strength is defined as <85% of the population-based value, according to Webb and colleagues (46). These sex- and age specific cut-off values are routinely being used in physiotherapist practices in the Netherlands.

Accelerometer data

To objectively assess the duration and intensity and distribution of physical activities and sedentary behaviour all patients are asked to wear an accelerometer on their wrist for seven consecutive days. Measurements will be in accordance with the schedule of the other measurements.

General physical performance

The performance status of patients during daily activities will be investigated using the Karnofsky performance scale. This is a scale ranging from 0 (dead) until 100 (normal general performance without complaints). An in- or decrease of 10 points will be used to detect significant differences. Furthermore, a timed sit-up-and-go test will be performed (47).

Body height and weight

Body height and weight will be measured on the described time points and body mass index (BMI) will be calculated.

Overall and disease-free survival

The possible effect of the intervention on overall and disease-free survival will be assessed on various time points (1, 3, and 5-years) after the intervention. Survival status will be extracted from the municipal registration system or the electronic patient file.

6.1.3 Other study parameters (if applicable)

Baseline parameters: gender, date of birth, weight, length, smoker status, level of education, marital status, ECOG status, est. weight loss last 6 months, comorbidities, diagnosis, TNM stage, tumor grade. date of surgery, surgery type, ASA classification, est. blood loss, radical resection, nr. nodes inspected, nr. nodes positive, hospital length of stay, Clavien-Dindo Classification and the Comprehensive Complications Index.

6.2 Randomisation, blinding and treatment allocation

Patients will be included on the preoperative surgical outpatient department. If at hospital discharge patients score ≥ 4 on the fatigue NRS , they will randomly be assigned to the treatment (rehabilitation program) or control (standard care) group in a 1:1 ratio.

Centralized stratified permuted block randomization will be performed by the Clinical Trial Center using the online ALEA software. The sample will be stratified based on organ (liver, pancreas, biliary tract) and organisation (EMC, LUMC, AMC, UMCG). Block randomisation within each stratum will be performed using variable block sizes ranging from 2 to 4. Neither patients nor therapists will be blinded for the treatment group. All therapists will be blinded for the NRS fatigue score that will be obtained before the start of the rehabilitation program.

6.3 Study procedures

The intervention will be offered close to the patients home. Patients in the control arm are offered standard medical care according to the local protocols.

- ***Dietary Intake***

  At discharge all patients will visit a dietary professional to assess their protein and caloric intake.

- ***Physical exercise therapy***

  The physical exercise therapy program will start four weeks after hospital discharge for duration of 12 weeks. The intervention group is offered a supervised and personalized exercise program that is aimed at both cardiorespiratory fitness (aerobic training) and muscle strength (resistance training) (48), which is also considered feasible in patients receiving chemotherapy (30). The program is developed in a close collaboration between physiotherapists, exercise physiologists, revalidation specialists, and medical and surgical oncologists. For each patient, an intake or baseline exercise measurement (i.e. 6 minute walk test and muscle function tests) will be performed at their medical center. Subsequently, the program will be specified to each patient's personal preferences and physical fitness with their physiotherapists. Hereafter, patients will train twice a week for one hour under supervision of a physical therapist. Patients are offered the following program: muscle strength training for 30 minutes per session. One training session exists of a minimum of six exercises: 1. Vertical row (longissimus, biceps brachii, and rhomboideus); 2. Leg press (quadriceps, glutei, gastrocnemius); 3. Bench press (pectoralis major, triceps); 4. Pull over (pectoralis, triceps brachii, deltoideus,

trapezius); 5. Abdominal crunch (rectus abdominis); 6. Lunge (quadriceps, glutei, hamstrings). For each exercise 3 sets of 8-12 repetitions should be performed. The training load should be adjusted up wards if a patient can perform more than 12 repetitions, and lowered if a patient can perform less than 8 repetitions. Aerobic training will be performed for next 30 minutes. The intensity of the training should be adjusted according to the Borg scale of perceived exertion, resulting in an exercise intensity of around 14. The maximum experienced workload will be 50-80% of the patients maximal physical capacity. The heart rate should be between 60-90% of the maximum heart rate. The maximum heart rate is approximated by subtracting the patients age from 220 (30). Patients will be informed about and motivated to perform daily exercise according to the Dutch Consensus on Healthy Exercise (49).

- ***Solution focused (psycho)therapy***

  Solution focused therapy has empirically been validated and shown successful in patients with chronic diseases (50). Furthermore, it has improved symptoms of fatigue in patient populations with somatic diseases, such as patients with inflammatory bowel disease, by our research group (23, 24). It was considered more feasible with fewer drop outs than problem solved therapy (24). Contrary to other forms of psychotherapy, solution focused therapy is goal-oriented, future-focused and focuses on solutions to patients' problems rather than on their problems. This approach assumes that everyone has some knowledge of what would make their life better, as well as some necessary coping skills. It is a short-term psychological intervention during which patients will be offered various interventions to channel their attention towards constructing solutions, including: goal setting, compliments, miracle questions, scaling questions, coping questions, and exception questions. The solution focused therapy will be offered in six sessions of one hour during twelve weeks and will be organised at the patients home following a similar structure as used by "Nierteams aan Huis".

6.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

6.5 Replacement of individual subjects after withdrawal

Withdrawn subjects will not be replaced.

6.6 Follow-up of subjects withdrawn from treatment

Overall- and disease free survival will be assessed.

6.7 Premature termination of the study

Although we have currently no reason to believe that the intervention is too intensive for the patients to be included, the study will prematurely be terminated when the intervention seems to be unfeasible.
If the drop out of included patients exceeds the estimated dropout rate and inclusion of patients within the given study period will not be possible, the study will prematurely be terminated.

7. SAFETY REPORTING

7.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to [the investigational product / trial procedure/ the experimental intervention]. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

7.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

7.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

7.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

7.5 [Data Safety Monitoring Board (DSMB) / Safety Committee]

Not applicable.

8. STATISTICAL ANALYSIS

All data will be collected in an electronically secured safe environment for the participating centres (Open Clinica). Statistical analyses will be performed using SPSS statistical software. Data will be analysed on an intention to treat basis. Adjusted analysis with prognostic baseline characteristics (gender, age, education, marital status, disease stage, radicality of resection) will be performed. This results in increased statistical power, corrects for baseline differences (based on chance) and provides better individualized treatment effect estimates (51). Two-sided p-values <0.05 will be considered significant and clinically important changes will be estimated as effect sizes using Cohen's guidelines. An effect size of 0.2 will be considered as small, 0.5 as medium, and 0.8 as large.

8.1 Primary study parameter(s)

The primary end point is the MFI-General Fatigue score measured at 12 months after surgery as described earlier. Superiority of the intervention group versus the control group will be assessed using a Mann-Whitney U to test if the two independent samples come from the same distribution.

8.2 Secondary study parameter(s)

Baseline characteristics will be compared between the intervention group and the control group with the independent Student's t-test or the Mann-Whitney test in case of continuous outcome variables and the Chi-square or Fisher's exact test in case of categorical outcome variables where appropriate. A linear mixed model will be used to assess and compare trends in longitudinal fatigue and quality of life data between the two groups, as well as measures of skeletal muscle mass and function, depression and anxiety, frailty, and functional capacity.

Cost-effectiveness analysis

A cost-utility analysis will be performed to identify the most cost-effective treatment (i.e. standard care or rehabilitation program), according to the Dutch guidelines. Both societal and healthcare provider perspectives will be addressed. The time horizon will be 12 months from surgery. The quality of life and costs will be assessed for each study arm. QALYs (based on the EQ-5D-5L) will be the outcome measure for quality of life and costs per QALY for the effectiveness analysis. If no differences in QALYs between the treatment arms are found, a cost-effectiveness analysis will be performed from both societal and healthcare provider perspectives, based on the QLQ-C30. The incremental cost-effectiveness ratios (ICERs), defined as differences in costs of the rehabilitation arm versus the standard care arm divided by the average change in QALYs or HRQoL, of the

arms will be calculated. Sensitivity analyses will be performed to test the sensitivity of various costs per unit of resource. No discounting for costs and effects will be used, due to the relatively short time horizon of 12 months. Direct and indirect costs will be accounted for in the cost analysis and estimated by multiplying resource utilization with the cost per unit of resource following the micro-costing method which is based on comprehensive 'bottom-up' analyses and included costs of employment, material and equipment. In other words, direct costs of each treatment arm will be accounted for. Hospital databases will be used to collect costs. Direct non-medical costs (e.g., travel costs of patients) will be determined using ZIP (postal) codes. The SF-HLW and friction cost approach will be used to take the indirect non-medical costs into account. Sensitivity analyses will be performed for uncertain and variable input variables to perform robust calculations. The cost-effectiveness analysis has been discussed with a healthcare economist.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (59th World Medical Association General Assembly, Seoul, October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO). This study will be performed with approval by the medical research ethics committee (MREC); in Dutch: Medisch Ethische Toetsings Commissie (METC). Approval of the METC will be requested as soon as possible after submission of this project plan. Participation in this study will be on a voluntary basis. If patients do not wish to participate, they can do so without specifying why. Deciding not to participate in the study will not affect regular treatment and follow-up care. Participants will be allowed to withdraw from the study at any time after they have given their written consent (see details Study Procedures). Study results will be published in (inter)national journals and presented at (inter)national conferences.

9.2 Recruitment and consent

Patients will be included on the preoperative surgical outpatient department and with hospital discharge patients will be asked to give written informed consent. Randomization will then be performed.

9.3 Benefits and risks assessment, group relatedness

N/A

9.4 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

9.5 Incentives (if applicable)

Compensation for travel expenses will be provided.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be handled confidentially. A subject identification code list will be used to link the data to the subject. These codes are not based on the patient initials and birth date. The key is safeguarded by the investigator. The handling of personal data is in compliance with the Dutch Personal Data protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wpb)

10.2 Monitoring and Quality Assurance

Monitoring will be performed following the Monitor Plan (appendix 1) as stated in the Risico A instructions, at least once a year by independent personnel of the Research office of the department Surgery Erasmus MC.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

The study will be registered in a public trial registry. Results will be made publically available according to the CCMO publication statement (available from www.ccmo.nl).

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

Not applicable.

11.2 Synthesis

Not applicable.

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APPENDIX 1

MONITORPLAN

WMO-plichtig onderzoek
Erasmus MC is verrichter

ALGEMENE GEGEVENS ONDERZOEK

NL nummer (ABR)	NL64296.078.17
MEC nummer	
Erasmus MC Afdeling	Heelkunde
Hoofdonderzoeker Erasmus MC	Prof.dr. J.N.M. IJzermans
Protocol code nummer / acroniem	CREST study
Cancer Rehabilitation in hepatopancreatobiliary cancer patients undergoing Surgical Treatment in an early palliative phase (CREST study)	

BEPALING RISICOCLASSIFICATIE

a. Bepaal het risico voor de patiënt aan de hand van de NFU tabel:

Mate van Schade / GROOTTE VAN KANS	**Lichte Schade**	**Matige Schade**	**Ernstige Schade**
KLEINE KANS	Verwaarloosbaar risico	Verwaarloosbaar risico	Matig risico
MATIGE KANS	Verwaarloosbaar risico	Matig risico	Hoog risico
GROTE KANS	Matig risico	Hoog risico	Hoog risico

Resultaat risicoclassificatie patiënt:

☒ verwaarloosbaar risico
☐ matig risico
☐ hoog risico

b. Bepaal het risico voor de wetenschappelijke kwaliteit van de data:

Denk hierbij bijvoorbeeld aan de volgende punten:

- Is het protocol moeilijk uit te voeren, bijvoorbeeld omdat het in grote mate afwijkt van de reguliere diagnostiek en/of zorg?

- Zijn er andere knelpunten er ten aanzien van de betrouwbaarheid van de data en de wetenschappelijke kwaliteit? bijvoorbeeld erg uitgebreid CRF, weinig proefpersonen per centrum, ...

Resultaat risicoclassificatie wetenschap:

☒ verwaarloosbaar risico
☐ matig risico
☐ hoog risico

c. Het risico van het onderzoek volgt uit bovenvermelde risico's

Houd van de hierboven bepaalde risicoclassificaties de hoogste aan. Dit is de risicoclassificatie van uw onderzoek.

Resultaat beoordeling risicoclassificatie onderzoek:

☒ verwaarloosbaar risico
☐ matig risico
☐ hoog risico

MONITORING FREQUENTIE EN INHOUD

Het vastgestelde risiconiveau impliceert dat monitoring van dit onderzoek minimaal de activiteiten omvat die zijn vermeld in de betreffende bijlage:

- Onderzoek met verwaarloosbaar risico -> zie bijlage A
- Onderzoek met matig risico -> zie bijlage B
- Onderzoek met hoog risico -> zie bijlage C

Voeg de betreffende bijlage toe; deze bijlage maakt integraal onderdeel uit van dit monitoringplan.

ONDERTEKENING DOOR HOOFDONDERZOEKER:

NAAM: Prof. dr. J.N.M. IJzermans, transplantatie chirurg

FUNCTIE: Hoofdonderzoeker

HANDTEKENING: _____

DATUM ONDERTEKENING: _____

BIJLAGE RISICO PROFIEL A

Frequentie en Inhoud Monitoring voor
ONDERZOEK MET VERWAARLOOSBAAR RISICO

FREQUENTIE MONITORING: 1 visite per jaar per centrum.

INHOUD MONITORING

Studiedocumenten en afspraken

Controle aanwezigheid en volledigheid van het onderzoeksdossier Trial Master File en Investigator File.

Controle instructies studiepersoneel en afspraken over back-up door bevoegde collega's.

Patiënteninstroom, consent, compliance en Source Document Verification (SDV)

- Controle inclusiesnelheid en uitval percentage.
- Controle informed consent: steekproef: 10%.
- Controle in- en exclusiecriteria: steekproef: eerste 3 deelnemers, daarna 1-10%.
- Controle protocolcompliance: steekproef: eerste 3 deelnemers, daarna 1-10%.
- Source Document Verification (SDV) steekproef:1-10%; wordt uitgevoerd op basis van een van
  tevoren gedefinieerde lijst van variabelen - inclusief primair eindpunt - die in duidelijke relatie
  staan tot de veiligheid en geldigheid van het onderzoek.

Patiëntveiligheid (indien van toepassing)

- Controle (Serious) Adverse Event [(S)AE] reporting: steekproef 1-10 % van de proefpersonen.

Studiemedicatie of onderzoeksproduct (indien van toepassing)

- Controle welke instructies deelnemers meekrijgen m.b.t. studiemedicatie of onderzoeksproduct.

Studieprocedures

- Controle of instructies voor uitvoer van studieprocedures aanwezig zijn.

Laboratorium, apotheek en biologische monsters (indien van toepassing)

- Controle of laboratoria GLP gecertificeerd zijn.
- Controle of apotheken GMP gecertificeerd zijn.
- Controle verzameling, labelen en opslag van biologische monsters.

AANDACHTSPUNTEN

- **kwalificaties monitor**
- **terugkoppeling en follow-up van bevindingen van de monitor**
  - Termijn van beschikbaarheid monitoring-rapporten.
  - Acties naar aanleiding van verbeterpunten in monitoring rapport: binnen Erasmus MC en in
    andere deelnemende centra (in geval van multi center trial).

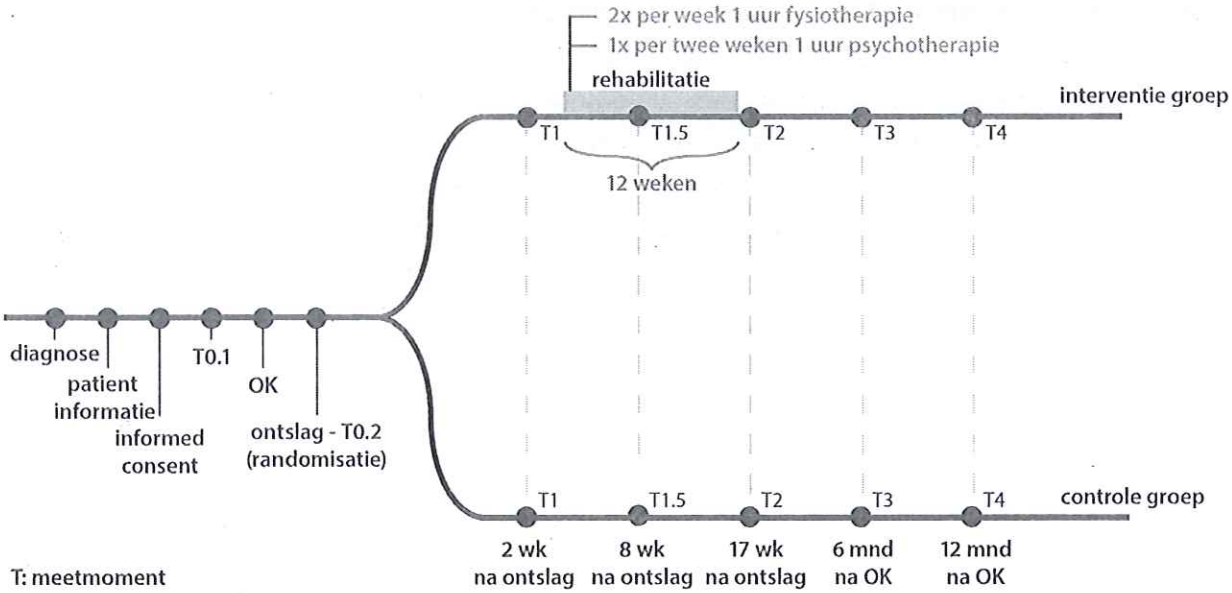
- **bewaren van studiegegevens**
  - Gebruik van een adequaat Clinical Data Management Systeem (CDMS).
  - Correct bewaren van ruwe gegevens, gecorrigeerde gegevens en back-ups.
  - Beschikbaarheid van een audit trail (herleidbaarheid van studiedata en aanpassingen).

MONITORINGRAPPORTEN EN BEWAARTERMIJN

Van elke monitoringvisit wordt een schriftelijk verslag gemaakt, het monitoringrapport. Het afdelingshoofd van de hoofdonderzoeker is verantwoordelijk voor de archivering van de monitoringrapporten gedurende minimaal 15 jaar na afronding van het onderzoek. De monitoringrapporten en overige onderzoeksdocumenten zijn op verzoek toegankelijk voor de Raad van Bestuur van het Erasmus MC, en voor door de Raad van Bestuur geautoriseerde.

APPENDIX 2

Overzicht metingen



Event \ Timeframe	*screening (T0.1)*	*surgery*	*Discharge (T0.2)*	*2 weeks after discharge (T1)*	*10 weeks after discharge (T1.5)*	*17 weeks after discharge (T2)*	*6 months after discharge (T3)*	*12 months after discharge (T4)*
Patient informed consent	x							
Assessment inclusion/exclusion criteria	x							
Registration baseline characteristics	x							
Registration surgical outcomes		x						
Registration recovery			x					
Height	x							
Weight	x			x		x	x	x
Karnofsky performance score	x			x		x	x	x
Timed sit-up and go test	x			x		x	x	x
6 Min. walk test				x		x		
Grip strength	x			x		x	x	x
Quadriceps peak force 5 seconds	x			x		x	x	x
8 day accelerometer tracking				x	x	x	x	x
Routine CT used	x			x		x	x	x
MFI questionnaire	x			x		x	x	x
EQ-5D-5L questionnaire	x			x		x	x	x
Life-C30 questionnaire	x			x		x	x	x
iVICQ questionaire (primary caregiver)	x						x	x
GFI questionnaire	x			x		x	x	x
HADS questionnaire	x			x		x	x	x
PG-SGA SF questionnaire	x			x		x	x	x
Diatary intake assesment			x					