AZIENDA USL DI FERRARA – AZIENDA OSPEDALIERO-UNIVERSITARIA DI FERRARA
DIPARTIMENTO INTERAZIENDALE DI CHIRURGIA
U.O. CHIRURGIA GENERALE DELTA – ARGENTA – U.O. CHIRURGIA 1 – U.O. CHIRURGIA 2

Studio Randomizzato Controllato sulla PREABILITAZIONE – Diagramma di Flusso							
	Preoperatorio			***Chirurgia***	***Postoperatorio***		
Settimane	**-5**	**-4**	**-1**	**0**	**4**	**8**	**52**
	Adesione	**Basale**	**Preoperatorio**	**Chirurgia**	**Follow up 30 giorni**	**Training 8 settimane**	**Follow up 1 anno**
Case manager	Inclusione	HRQoL QoL SF-36 GAD-7 PHQ-9	HRQoL QoL SF-36 GAD-7 PHQ-9	x	HRQoL QoL SF-36 GAD-7 PHQ-9	HRQoL QoL SF-36 GAD-7 PHQ-9	HRQoL QoL SF-36 GAD-7 PHQ-9
Medico dello sport	x	Consenso Informato VO2max Soglia Anaerobica Exercise-ECG 1RM* 6MWT Sit-to-stand test	Consenso Informato VO2max Soglia Anaerobica Exercise-ECG 1RM* 6MWT Sit-to-stand test	x	VO2max Soglia Anaerobica Exercise-ECG 1RM* 6MWT Sit-to-stand test	VO2max Soglia Anaerobica Exercise-ECG 1RM* 6MWT Sit-to-stand test	x
Nutrizionista/ Dietista		Diario dietetico Altezza, peso Calo ponderale %# Circonferenza polso/addome/avan braccio Plica del tricipite Forza presa mano PG-SGA score	Diario dietetico Altezza, peso Calo ponderale %# Circonferenza polso/addome/avanb raccio Plica del tricipite Forza presa mano PG-SGA score	x	Altezza, peso Calo ponderale % Forza presa mano PG-SGA score	Altezza, peso Calo ponderale % Forza presa mano PG-SGA score	x
Anestesista	x	x	Visita preoperatoria	ERAS**		x	x
Chirurgo	Informazione Adesione	x	ERAS**	x	Dati ambulatoriali	x	x
Ricercatore	x	x	x	x	Morbilità-mortalità a 30 giorni	Morbilità-mortalità a 60 giorni	Mortalità a 1 anno

*** Diverse misurazioni 1RM effettuate mediante: leg press, abdominal crunch, chest press and lateral pull down. ** Linee Guida Enhanced Recovery Afer Surgery (ERAS) . # calo ponderale negli ultimi 3--6 mesi**

- La fase di Adesione (– 5 settimane): nella nostra realtà viene condotta dal Chirurgo alla prima visita pre-operatoria.
  Il Nutrizionista/dietista può impostare il diario dietetico

- Nella fase Basale (– 4 settimane): il Medico dello Sport/Fisiatra somministrano il consenso informato alla fase di preabilitazione ed effettuano contemporaneamente i test ergometrici e la prima seduta di allenamento
  Il nutrizionista può effettuare le misurazione antropometriche
  Il Ricercatore/Case Manager somministrano i questionari: HRQoL, QoLSF-36 , GAD-7 ,PHQ9

- Nella fase preoperatoria (-1 settimana) le figure coinvolte nella fase basale effettuano test e misurazioni di loro competenza.

L'Anestesista effettua la visita pre-operatoria.
Il Chirurgo fornisce le informazioni necessarie al consenso informato sull'atto chirurgico e sulle procedure ERAS.

- Nella fase post-operatoria di Follow-up a 30 giorni, Medico dello Sport/Fisiatra effettuano test ergometrici e misurazioni.

Il Nutrizionista / dietista effettua le misurazioni antropometriche.
Il chirurgo fornisce dati clinici ambulatoriali ed il Ricercatore analizza i dati di morbilità.
Case Manager somministra il questionario QoL ed i questionari su ansia /depressione

Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and reduce postoperative complications (PREHAB)

The first international randomized controlled trial on multimodal prehabilitation

(June 2017)

PROTOCOL TITLE 'Multimodal prehabilitation in colorectal cancer patients to improve functional capacity and lower postoperative complications. ***The first international randomized controlled trial on multimodal prehabilitation*****'**

Protocol ID	NL58281.015.16
Short title	Prehabilitation for colorectal cancer patients
EudraCT number	Not applicable
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Date	April 5th 2017
Coordinating investigator	Dr. G.D. Slooter, surgeon

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Sponsor (in Dutch: verrichter/opdrachtgever)	Máxima Medical Center
Subsidizing party	Each center provides its own finance
Independent expert (s)	G. Vreugdenhil, MD PhD internal medicine
Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor or legal representative: *K. van Boxtel, manager Máxima Oncologisch Centrum* **Head of Department:** *R. Roumen* **Principal Investigator:** *G.D. Slooter*		

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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**
CAL	**Colorectal Anastomotic Leakage**
CCI	**Comprehensive Complication Index**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CPET	**CardioPulmonary Exercise Testing**
CRC	**ColoRectal Cancer**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
HRQoL	**Health Related Quality of Life**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
LOS	**Length of Hospital Stay**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
PREHAB	**Prehabilitation**
PROM	**Patient-reported Outcome Measurements**
(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: Colorectal cancer (CRC) is the second most prevalent type of cancer in the World. The only curative treatment is surgical removal of the tumor. However, postoperative complications occur in up to 50% of patients and are associated with a higher mortality- and return of cancer rate and increased hospital costs. The number and severity of complications is closely related to preoperative functional capacity, nutritional state and smoking behavior. Traditional approaches have targeted the per- and postoperative period for rehabilitation and lifestyle changes. However, recent evidence shows that the preoperative period might be the optimal time frame for intervention.

Objective: This study will determine the effects of multimodal prehabilitation on functional capacity and postoperative complications in patients with colorectal cancer.

Study design: International multicenter, prospective, randomized controlled trial.

Study population: Adult patients undergoing elective surgery for colorectal cancer.

Intervention: Patients will be allocated to an intervention group, receiving 4 weeks prehabilitation (group 1, prehab) or to the control group receiving no prehabilitation (group 2, no- prehab). Both groups obtain 8 weeks rehabilitation postoperatively following ERAS guidelines, which is standard care.

Main study parameters/endpoints: The primary endpoints are functional capacity, measured by the 6-minute walk test (6-MWT) and postoperative complications expressed by the Comprehensive Complication Index (CCI). Secondary outcomes include Patient Reported Outcome Measurements (PROMs) such as health related quality of life (HRQoL) (EORTC QLQ-CR29 and EORTC QLQ-C30, RAND questionnaires) and depression and anxiety scores (GAD-7, PHQ-9 questionnaires), functional capacity (VO2max, sit to stand test, stair climb test, hand grip strength and activity questionnaire), nutritional status, length of hospital stay, study compliance, patient satisfaction and a cost-effectiveness analysis.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: Side effects might be cardiac arrhythmias or other exercise related problems during the VO2 maximal intensity exercise tests. Exercise training is not expected to cause any risk to patients. However, since patients are thoroughly screened, we expect to find more pre-existing cardio-pulmonary conditions, for which patients will be referred to either a pulmonologist or cardiologist. The amount of tests might be perceived as a burden for the patients in both groups, as well as the amount of hospital visits for the prehabilitation group.

1. INTRODUCTION AND RATIONALE

Colorectal cancer (CRC) is the second most prevalent type of cancer in the World with over 800.000 patients diagnosed yearly. The only way to cure CRC is by surgical removal of the tumor. However, postoperative complications occur in up to 50% of patients and are associated with a higher mortality- and return of cancer rate, increased hospital costs and a lower Health Related Quality of Life (HRQoL).[1,2,3] Even in the absence of complications, major surgery is associated with a 20% to 40% reduction in physiological and functional capacity when measured by energy expenditure, endurance time, workload and heart rate during maximum exercise. This reduction in physiologic reserve is experienced as a higher level of fatigue 4-6 weeks after hospital discharge and a return to preoperative baseline functional capacity of only 40%.[4] The fact that the mean age of colorectal cancer patients is 70 years old, adds up to the risk of irreversible loss of functional capacity during hospital admission.

Fatigue following surgery is manifested by muscular weakness, increased need for sleep and decreased ability to concentrate. It is correlated with preoperative health status, preoperative fatigue, weight, and grip strength, the degree of surgical trauma and intensity of metabolic response, and with postoperative deterioration. Moreover, after operation many patients may need to undergo further treatment like chemotherapy and radiotherapy. This becomes more physically challenging if functional capacity is already lowered due to surgery. If functional capacity is improved preoperatively, postoperative recovery might be faster and adjuvant chemotherapy might be started earlier. This is important since it will result in an increase in survival as reported by recent research findings of the Dutch cancer registry. In this study, 11 000 CRC stage 3 patients were included (2008-2013). 4899 were not treated with chemotherapy and had a 5 years survival of only 39%. If chemotherapy started >12 weeks postoperatively, 5 years survival increased to 54%. Chemotherapy treatment started <6 weeks after operation 5 years survival was further increased to 76%.

Efforts to improve the recovery process have primarily focused on the intraoperative (e.g., minimally invasive surgery, afferent neural blockade) and post-operative periods (e.g., “fast track” early nutrition and mobilization[5]). The latter protocols have been designed to facilitate the return of functional activities and accelerate convalescence. However, the post-operative period may not be the best time to ask surgical patients to make significant changes in their nutrition and exercise, as patients are tired and concerned about perturbing the healing process as well as being depressed and anxious as they await additional treatments for their underlying condition. The pre-operative period may in fact be a better time to intervene in the factors that contribute to recovery beyond the physical and alleviate some of the emotional distress surrounding the anticipation of surgery and the recovery process.[6] The process of enhancing functional capacity of the individual to enable him or her to withstand an incoming stressor has been termed *prehabilitation*.[7,8] Although some have used education to prepare patients for procedures,[9] little has been developed to systematically enhance functional capacity before surgery.

Factors that are strongly associated with complications after colorectal surgery are poor physical condition, nutritional status, cigarette smoking and mental status, and will be individually explained below.

Functional capacity

It has been shown that poor baseline physical performance capacity increases the risk of complications after major non cardiac surgery and prolongs recovery after abdominal surgery. A review on the role of optimizing functional exercise capacity in the surgical population indicated that this approach can result in fewer postoperative complications, shorten the length of hospital stay, reduce disability, and improve quality of life, compared to controls.[10] Based on the notion that preoperative exercise would have an impact on recovery of functional capacity after colorectal surgery, a randomized controlled trial has been performed by Carli et al. This trial, the first and largest trial on surgical prehabilitation, compared two exercise regimens (intense exercise on a stationary bike *vs* walking and deep breathing) for several weeks before colorectal surgery. The primary outcome was functional walking capacity measured by the six-minute walk test (6MWT) between 5 to 9 weeks postoperatively. Subgroup analysis identified that patients whose functional exercise capacity improved preoperatively, regardless of exercise technique, recovered well in the postoperative period. However, one-third of patients deteriorated preoperatively despite the exercise regimen, and these patients were also at greater risk for prolonged recovery after surgery. Poor preoperative physical function (fatigue, malnutrition and physical performance) and presence of anxiety and depression were also significant confounding predictors of prolonged recovery. These results suggest that exercise training alone is not sufficient to attenuate the stress response in all patients and that it is important to address also factors that promote the beneficial adaptations to training like nutrition and coping behavior. Therefore a new multimodal prehabilitation program was developed multidisciplinary in the Máxima Medical Center together with prof. Carli for the PREHAB trial.

Nutritional status

The role of nutritional status in surgical recovery cannot be underestimated. Evidence from cardiac rehabilitation suggests that exercise attenuates fatigue by facilitating the incorporation of nutrients in tissues and improves quality of life by reducing the impact of anxiety and depression.[11] The nutritional status of patients affected by colorectal cancer is directly influenced by the presence of cancer which impacts on all aspects of intermediary (protein, carbohydrate, lipid, trace element, vitamin) metabolism, and by other factors such as age, adjuvant cancer therapy, stage of the disease and by complaints like nausea and fatigue. The greater sensitivity of protein catabolism to nutritional support, in particular to amino acids, could have important implications for the nutritional management of these patients during the period of catabolic stress, with particular emphasis on substrate utilization and energy requirement.[12]

Because most patients are able to eat normally before elective colorectal surgery, and the absorptive capacity of the bowel is not impaired, many CRC patients have seemingly normal preoperative nutritional status.[13,14] However, consumption of energy and protein is often low in patients about to undergo colonic surgery and malnutrition or unintended weight loss occurs in up to 36,4% of CRC patients.[13,15,16,17,18,19] In undernourished patients, especially loss of lean body mass (muscle mass) is associated with adverse outcome. In oncology patients, the presence of low lean body mass may be related to lower tolerance to (neo)adjuvant therapy.[20,21] Furthermore, malnutrition with unintended weight loss and/or low lean muscle mass in (CRC) surgery patients is associated with more post-operative complications, delayed recovery of bowel function, prolonged length of hospital stay, higher re-admission rates, higher costs, reduced quality of life, and higher incidence of postoperative morbidity and mortality.[13,22,23]

Emerging is that a normal or high body weight, occurring in most CRC patients, may hide underlying muscle wasting.[13] Most of CRC patients are 60 years or older, and in this age group anabolic resistance is known to be highly prevalent. Anabolic resistance implies a reduced capability to synthesize muscle protein in reaction to anabolic stimuli (i.e. exercise and protein) and results in muscle wasting. Inflammatory disease, reduced physical activity and inadequate intake of energy, protein and vitamin D enhance the age-related loss of muscle mass, also known as sarcopenia (loss of muscle mass with increased or stable fat mass).[24,25,26,27]

Sarcopenia and sarcopenic obesity (sarcopenia in combination with high body weight) are associated with reduced muscle strength, functional decline, physical disability, increased risks of fractures and falls, enhanced risk of metabolic disease, increased length of hospital stay and decreased survival in general populations of older adults.[25,28,29,30]

Preoperative nutritional intervention in malnourished patients with unplanned weight loss, aiming improvement of nutritional status, has been shown an effective strategy for reducing risk of post-surgery complications such as infections and anastomotic leaks.[13]

Preoperative nutritional interventions focusing on improvement of lean body mass in CRC patients with sarcopenia or sarcopenic obesity in order to improve post-surgical outcome, have gained less attention.

Cigarette smoking

Cigarette smoking itself is a well-known risk factor for postoperative complications. Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complication.[31] Wound contraction and collagen metabolism are also affected by a smoking-induced alteration in vitamin C turnover and by a change in inflammatory cell response.[32] Evidence exists that preoperative smoking interventions reduce postoperative morbidity. Moreover, smoking cessation restores the tissue microenvironment rapidly and the inflammatory cellular functions within 4 weeks. Therefore, smoking cessation a few weeks before surgery is likely to reduce the risk of all complications, as well as the major complication CAL. A period of 4 to 8 weeks smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications.[33]

Mental status

Psychological status may also play an important role in surgical recovery. It is well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery.[34,35] They may also feel depressed, hold unrealistic expectations (overly optimistic or pessimistic) about their health status, and possess inadequate strategies for coping with pre- and post-operative periods. Any of these factors may influence pain[36] and interfere with post-operative functioning.[37,38]

Multimodal prehabilitation

Although exercise, nutritional interventions, smoke cessation and psychological interventions prior to surgery have separately shown to improve several post-surgical outcome parameters, no studies have been performed investigating a *combined* multimodal intervention approach in preoperative CRC patients. This is a huge gap in our knowledge. It is already known that a strong interaction exists between exercise and nutrition, and their synergistic effects on muscle protein synthesis have been associated with gains in muscle mass, increased muscle strength, improved functional capacity and better functional performance in studies among other older populations.[39]

When physical activity is performed closely before ingestion of a meal-like amount of dietary protein, the blunted anabolic response in healthy older individuals can largely be overcome.[40] A protein enriched diet with protein supplementation during resistance training programs has been shown to enhance fat free mass,[41, 42] improve 1-RM leg press strength (the maximum weight a person can press with his/her leg,[41] and preserve muscle mass even during intentional weight loss intervention.[27]

Protein is the fundamentally anabolic nutrient.[43] Besides protein ingestion immediately post-exercise (30-40 g), a higher overall dietary protein intake, ample protein consumption evenly divided across all meals (25-30 g per meal) and protein ingestion before sleep are associated with a prolonged anabolic effect of physical training. Importantly, studies have demonstrated that with ample amounts of amino acids, an anabolic state can be obtained even in patients with cancer.[44] Finally, vitamin D is associated with muscle mass and strength.[45, 46, 47]

Since it has been established that the number and severity of complications is closely related to preoperative functional capacity, nutritional status, smoking behavior and psychological well-being, there is a growing need to target these issues by means of the implementation of a multimodal intervention program. From a physiological point of view and based on limited practical experience, it seems feasible to achieve clinically relevant effects during the frame of 4-5 weeks between diagnosis and operation. However, this will only be achieved if targeted interventions involving exercise, nutrition, smoke cessation and psychological support are implemented.[48,49,50,51,52]

2. OBJECTIVES

Primary Objective: To investigate if multimodal prehabilitation could decrease postoperative complications and improve functional capacity pre- and postoperatively for patients undergoing colorectal surgery for cancer.

Secondary Objective(s): To investigate the effects of multimodal prehabilitation on Health Related Quality of Life, nutritional status, length of hospital stay and cost-effectiveness.

3. STUDY DESIGN

This is an international multicenter, randomized controlled trial with two randomized groups. Patients of adult (>18 years) age undergoing elective colorectal resection for cancer are eligible for inclusion. A total of 708 patients will be included in six participating centers (Copenhagen, Veldhoven, Montréal, Barcelona, Ferrara, Paris). Study will aim to start may of 2017 in Máxima Medical Center, Veldhoven, The Netherlands, and in Montréal General Hospital, Canada, and in 2017 in the other participating centers. Inclusion of patients will take approximately 2 years and the follow-up is 1 year.

The control group in this study will receive standard care according to international ERAS protocol.

An overview of the measurements during the PREHAB study can be found in appendix I. These measurements will be applied in the control group as well as the intervention group.

4. STUDY POPULATION

4.1 Population (base)

Colorectal cancer patients in Máxima Medical Center, scheduled for elective surgery.

4.2 Inclusion criteria

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

Adult patients (>18 years) undergoing elective colorectal surgery for cancer.

4.3 Exclusion criteria

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

- metastatic disease known preoperatively,
- paralytic or immobilized patients (not capable to perform exercise or 6MWT),
- premorbid conditions or orthopedic impairments that contraindicated exercise,
- cognitive disabilities,
- chronic renal failure (dialysis or creatin > 250 mmol)
- ASA score 4 or higher,
- illiteracy,
- abdominoperineal resection (inability to perform postoperative tests).

4.4 Sample size calculation

The sample size calculation is based on the primary aim, to lower postoperative complications as determined according to the CCI score. With our population variables, CCI mean is 10.4 (SD 14), aiming to see decrease of 30%. We use an alpha of 0.05 and power of 0.80 (two-sided test). 10% dropouts are expected. We than need 708 patients, 354 per arm. This gives us a 100% efficacy to see a 6MWT proportion of improvement difference (55% versus 20%) as observed in previous studies.[7,8] Each year around 800 eligible CRC patients undergo surgery in the participating hospitals in total, indicating that we will finish inclusion within 2 year time, with subsequent follow-up of 1 year.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

1. Patient triage medical conditions

Patient triage will allow us to tailor perioperative management, which may lower the risk for postoperative complications 30% in 'the risky' group. An anaerobic threshold (AT) value of the VO2max test of 10 ml/kg/min gives 0.88 specificity and 0.79 sensitivity with area under curve of 0,85 for risk of complications.[53] Also severe pulmonary and cardiac disease will often be detected and scaled upon severity with exercise testing.

Triage will also focus on anemia, to identify patients' cardiopulmonary comorbidity using VO2 peak tests. Patients will be screened preoperatively (4 weeks before surgery) to capture insufficient hemoglobin levels (thresholds in Canada: >11.2 g/dl, Europe: >7mmol/l). In case of iron insufficiency, hemoglobin levels will be optimized using iron injections. In combination with training it may give substantial effect.

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Triage described above will be applied to the intervention group as well as controls.

2. Prehabilitation intervention

The intervention described below will only be given to the intervention arm of this study. The only exception is the smoke-cessation program, which will be offered to all patients.

Exercise program

An exercise specialist (kinesiologist, sport physician) will assess patients' mobility and capacity to undertake exercise. All participants will undergo a cardiopulmonary exercise test (CPET) and the exercise intensity will be defined and personalized on the individual CPET values. Based on the evaluation, a, personalized program from the standardized program will be coordinated, as defined in appendix II. Additional to the preoperative exercise program, patients will receive information regarding breathing techniques to prevent occurrence of pneumonia.

With the intervention we try to achieve a maximum training stimulus in combination with a recovery diet, in order to achieve these goals in 4 weeks. The program exists of several components:

- Strength training and high intensity interval training: this will be done 3 times a week supervised in the hospital. The strength training consists of 2 series of 10 repetitions of 6 exercises targeting all major muscle groups. The high intensity interval training aimed at 90% of the VO2-peak
- Homework endurance training (low to moderate intensity): 4 times a week done at home.
- Diet and rest: the diet is focused on a protein intake of 1,5-1,8 g/kg/day with 0,4 g/kg/day whey proteins after training and 0,4 g/kg/day casein proteins before bedtime. This is further explained in the nutrition section of the protocol.

With the training program we try to achieve the following improvements:

- Increase of 10% of VO2-peak
- Increase of 15% of VO2-peak at AT
- Increase of 20-40% in 1RM tests (or increase in dumbbell weight)
- Increase in the distance of 10% at 6MWT (at <500m)
- Decrease of 10% of the stairs climb test

At baseline, after prehabilitation (1 week before surgery) and 4 weeks after surgery CPET will be performed. At baseline, the week before surgery, 4 and 8 weeks postoperatively, muscle strength will be tested with the sit-to-stand test, 1-RM and handgrip strength. Functional capacity will be tested at the same time points using the 6-minute walk test and stair climb test. Patients in both groups will wear an accelerometer during four weeks before surgery and four weeks after surgery in order to estimate (changes) in physical activity outside of the hospital in the control and intervention group.

Determine AT:

While slowly increasing the resistance, the VO2, VCO2 and VE (expired ventilation) will initially rise linear, up to the moment lactic acidosis develops. With effort above the anaerobic threshold (AT) the CO2 rises faster than the O2 uptake, because the CO2 produced from $HCO3^-$, by buffering lactate, is added to the CO2 production. VE rises with the increase of CO2 output (isocapnic buffering), there is still a linear relation whereby EQCO2 (VE/VCO2) remains constant (or a light decrease), while EQO2 (VE/VO2) increases.

- Increase of VE/VO2, while VE/VCO2 remains constant (or light decreases).
- Increase of PETO2 (change in linearity) vs workload.
- V-slope: change in linearity of VO2 vs VCO2

Determine RCP:

If the workload (Watt) after AT further increases, VE rises faster than de CO2 output, i.e. a rise of EQCO2 (VE/VCO2), which ensures for a decrease of PaCO2 and PETCO2 (hyperventilation). The point at which the VE rises more than needed for the CO2, and the PETCO2 decreases is a 'extra' ventilatory response and is also called 'respiratory compensation point' (RCP). The increase of H+ concentration stimulates the carotic bodies (vascular glands) to increase the ventilatory drive as a reaction at the lactic acidosis. By an increase of VE the arterial PCO2 decreases.

- Increase of VE/VCO2 vs workload
- Decrease of PETCO2 vs workload.
- VE vs VCO2: change in linearity

Nutritional supplements

To enhance the anabolic effect of physical training, improve lean body mass and obtain or maintain an optimal nutritional status during the prehabilitation period, sufficient intake of nutrients (especially energy and protein) is required. The schedule for the nutritional intervention can be found in Appendix III.

A registered dietician will assess patients' nutritional status at baseline and at the end of the exercise program, using the Patient Generated Subjective Global Assessment (PG-SGA). Furthermore, a set of anthropometric measurements (including body weight, length, triceps skinfold, hand grip strength and circumferences of wrist, waist and upper arm) is performed to allow assessment of (change in) body weight, (subcutaneous) fat mass, (upper limb) muscle mass and muscle strength, taking into account patients' body frame.

The patient will fill in a three-day food diary (including two week days and one weekend day), which will provide an estimate of habitual macronutrient consumption[54] as analyzed using a commercially available software program.[55] Based on estimated habitual protein intake, participants will receive a tailored dietary advice aiming a total protein intake of 1,5 (- max 1,8) gram / kg daily.[56,57] Also, patients will be recommended to evenly 'spread' their protein intake over 3 meals with a minimum of 25-30 gram of protein/ meal.[58] To stimulate muscle protein synthesis, participants will also be provided with a protein (0,4 gram/kg/day) supplement immediately after strength training (3 times a week) and daily before sleep.

Patients' energy requirements will be estimated according to the revised Harris and Benedict equation[59] using stress- and activity factors between 1,3 and 1,5. Recommendations to change energy intake will not only be based on discrepancies between estimated energy intake and energy requirements, but also on (changes in) nutritional status parameters, such as weight loss. This is done because underreporting of true energy intake is commonly seen with self-reported dietary assessment[60, 61] and can increase up to 50% in overweight people.[62]

Since vitamin D is associated with muscle mass and muscle strength,[63, 64] vitamin D will be supplemented daily according to guidelines of the Health Council of the Netherlands (10 µg for women aged 50-69y, for men <70y and women <50y with colored skin and/or little sun exposure and 20 µg for women and men aged 70 y or older).[65] Besides vitamin D, many elderly patients may have other micronutrient deficiencies or ingest vitamins and minerals below recommended doses before and after surgery. Therefore, all other vitamins and minerals are supplied in a multivitamin/mineral supplement containing 50% of the recommended daily allowance.

During the period of hospitalization, the time (in days) that patients consume nil per mouth is recorded. Also, on the day of discharge, a trained dietician performs a 24-hour recall questionnaire to estimate oral protein- and energy intake.

Nutritional status assessment (PG-SGA and weight gain or loss) will be performed at 4 and 8 weeks post-surgery by an investigator – trained by a registered dietician.

Protein supplementation

Resistance training and protein supplementation have synergistic effects on muscle protein synthesis.[25,43,66,67] In young healthy men, consumption of as little as 20-25 g of protein immediately following physical activity has shown to improve muscle accretion.[68,69,70] Due to anabolic resistance, elderly subjects require higher amounts of protein to obtain exercise-induced anabolism. Studies show that ingestion of 30-40 g of high quality dietary protein immediately after a bout of exercise may best support reconditioning in older adults.[71] Furthermore, the amount and amino acid composition of the post-exercise protein source is of particular importance. An amount of 6-10 g of essential amino acids (EAA) has shown to optimally stimulate muscle protein synthesis in healthy young men.[72] Of all EAA, especially leucine appears to be a strong stimulus for protein synthesis. It is suggested that the post-exercise protein source should contain 2-3 g of leucine in both young and older adults[73, 74] The exercise-induced enhanced sensitivity to the anabolic properties of amino acids in muscle mass is retained for at least 24 hours following physical activity. Studies have shown that ingestion of protein before sleep may prolong muscle protein synthesis during overnight post exercise recovery.[75]

Therefore, participants of PREHAB Intervention group will receive protein supplementation immediately following exercise and (± 30 minutes) before sleep, providing a standard dosage of 25 g of a high quality protein source that contains at least 10 g of EAA, of which 2-3 g leucine.

Smoke cessation

Cigarette smoking itself is a well-known risk factor for postoperative complications. Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complications.[76] A period of 4 to 8 weeks

smoking cessation prior to surgery has already been shown to significantly reduce postoperative complications and morbidity.[77] A smoke cessation program including intensive counseling and nicotine replacement therapy (NRT) will be offered to all patients – including patients in the control group – during the 4 weeks prior to the surgery. Approximately 15-20% of our patients are current smokers at the moment of cancer diagnosis. The goal is to achieve a smoke cessation percentage of 80 before surgery.

Psychological coping

It is expected that patients undergoing surgery for cancer are anxious with some component of depression. Since both anxiety and depression can influence the motivation to carry out social and functional activities, psychological strategies can be put in place to help patients to cope with the stress of surgery and disease. Therefore, patients will be screened for anxiety and depression using the GAD-7 and PHQ-9 questionnaires. If these questionnaires result in a high score (GAD-7 of 10 or higher; PHQ-9 score 15 or higher), patients are considered high-risk and will be offered a referral to a psychologist. Referred patients will receive a total of 1.5 hours of psychological intervention in the first session and more sessions during the 4 weeks of prehabilitation if necessary. In this preoperative session, the first hour will address the patient's anxieties, coping strategies, and post-operative expectations, with the goal of optimizing psychological well-being & ways of coping with surgery. The importance of the patient's active participation in the healing process will also be discussed.

All patients in the intervention group will be given instructions on relaxation and breathing techniques by a trained investigator. They will be given an instruction CD, which they can use for relaxation techniques at home. After the program, patients will be asked if their perceived usefulness of these techniques.

Also, as a form of psychological support, the intervention group will be contacted weekly by the investigator by phone. During these 5-15 minute phone calls, a researcher will shortly evaluate the following themes:

- General health perception of the patient: "how are you doing?"
- Evaluation of anxiety and use of anxiety reduction techniques.
- Evaluation of training: attendance, side effects/injuries, factors limiting attendance or completion of exercises.
- Evaluation of dietary intervention (protein supplement and advice): evaluate adherence and side effects.
- If relevant: smoking-cessation. Perception of usefulness of the program, smoking status (active smoker/stopped?), side effects.
- Any other questions the patient may have.

In order to enhance adherence to the prehabilitation program, all patients in the intervention group will receive an instructional brochure that includes information about all elements of the program.

5.2 Use of co-intervention (if applicable)

Not applicable.

5.3 Escape medication (if applicable)

Not applicable.

6. INVESTIGATIONAL PRODUCT

Not applicable.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable.

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The first primary outcome is postoperative complications as measured by the Comprehensive Complication Index score, a combined outcome measure of morbidity and mortality.[78]

The second primary/confirmatory outcome is the patients' functional capacity 8 weeks postoperatively, as measured by the six-minute walk test (6MWT).

8.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes include Patient Reported Outcome Measurements (PROMs) such as health related quality of life (HRQoL) (EORTC QLQ-CR29 and EORTC QLQ-C30, RAND questionnaires) and depression and anxiety scores (GAD-7, PHQ-9 questionnaires), functional capacity (VO2max, sit to stand test, stair climb test, 1-RM, hand grip strength and self-reported physical activity), nutritional status, length of hospital stay, study compliance, and a cost-effectiveness analysis.

8.1.3 Other study parameters (if applicable)

Surgery and anesthesia care

Surgery will be performed in all institutions by one of the three/four colorectal surgeons. Surgical approach, including laparoscopic or open surgery, stoma placement, etc will be at the discretion of the surgeon. Perioperative care will follow the Enhanced Recovery After Surgery (ERAS) program, which is an evidence-based multidisciplinary care plan.[79] The ERAS for colorectal surgery started to be operational since several years in all participating centers and regroups all the colorectal surgeries, and includes patient education, preoperative feeding, selected bowel preparation, laparoscopic approach, multimodal analgesia, maintenance of perioperative normothermia, early oral intake and early mobilization, early removal of catheters and drains, and a planned 3-5 day hospital stay.

We add chewing gum and coffee drinking to the current ERAS program, since they have both been investigated as beneficial improving recovery of patients bowel function.[80]

8.2 Randomization, blinding and treatment allocation

Patients will be randomized by block randomization with a block size of 8, with a 1:1 allocation by means of randomization software, stratified by study sites, neoadjuvant therapy vs. no neoadjuvant therapy and tumour location (colon/rectum). Patients will be allocated either to the prehabilitation intervention group, receiving 4 weeks prehabilitation, or to the control group, receiving no prehabilitation (standard care). Both groups will receive 8-week rehabilitation following the current international ERAS guidelines. Similarly all the perioperative care will follow the ERAS guidelines for colorectal surgery.

8.3 Study procedures

- The Clavien Dindo classification is correlated with the complexity of the operation as well as the length of hospitalization and may be used internationally as quality screening for surgery[81,82]. The Comprehensive Complication Index summarizes the postoperative wellbeing of the patient concerning complications based on the Clavien-Dindo classification[83]. The CCI-score is easily assessed at www.assessurgery.com. Both scores will be determined at four weeks after surgery.

- The 6MWT evaluates the ability of an individual to maintain a moderate level of physical activity over a time period reflective of the activities of daily living.[84] Subjects are instructed to walk back and forth, in a **20 m stretch of hallway**, for six minutes, at a pace that would make them tired by the end of the walk; encouragement and feedback are given according to published guidelines. They are allowed to rest during the test if needed, but this time is included in the 6 minutes. Reference equations are available for calculating percent of age- and gender-specific norms.[85] In community dwelling elderly, measurement error was estimated at 20 meters and this will be used as the threshold value for determining true change. The 6MWT correlates moderately with VO_2max indicating that these two tests measure related but not identical constructs. As daily activity is mostly pursued at a sub-maximal level, functional walking capacity is a more direct measure of capacity for daily routine than a maximal test of exercise capacity such as VO_2max and is more feasible to perform in the perioperative population. The test-retest reliability has been reported to range from 0.73 to 0.99 among a variety of populations, including the elderly. The 6MWT has been shown to be reliable and valid in many populations including surgical ones, with a recent paper supporting its validity as a measure of recovery after colorectal surgery.[86] The 6 minute walk test will be administered at baseline, after completion of the prehabilitation program, and at 4 and 8 weeks after surgery to assess the impact of the intervention throughout the perioperative period.

- CPET serves as a gold standard and provides assessment of the integrative exercise responses involving the pulmonary, cardiovascular, hematopoietic, neuropsychological, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.[87] This non - invasive, dynamic physiological overview permits the evaluation of both submaximal and peak exercise responses, providing the doctor with relevant information for clinical decision making. CPET is increasingly being used in a wide spectrum of clinical applications for the evaluation of undiagnosed exercise intolerance and for the objective determination of functional capacity and impairment. Its use in patient management is increasing with the understanding that resting pulmonary and cardiac function testing cannot reliably predict exercise performance and functional capacity and that overall health status correlates better with exercise tolerance than with resting measurements. CPET parameters (ECG, VO2max, HF, AT, RQ) will be administered at baseline to establish exercise intensity, after prehabilitation (1 week before surgery), and at 4 weeks after surgery to assess the impact of the intervention.
- Muscle strength

  Hand grip strength test can be used to characterize general upper extremity muscle strength,[88,89,90] and can increase after general upper extremity resistance training including exercises that did not specifically involve handgrip strength.[91] Upper extremity muscle strength of adults is measured using a JAMAR grip strength dynamometer.

  Stair climb test has the time needed to climb a stair as the basic variable. Together with the vertical displacement and body weight, the stair climb power is calculated.[92] This value is normalized by body weight. The test-retest reliability of the 10-step stair climb power test in a population of elderly people (range 65-94 years) is very high (*r*=0.99).[92] Leg press power at 40% of 1RM weight showed a correlation of *r*=0.47 (P<0.001) with the stair climb power. Leg press power at 70% of 1RM weight showed a correlation of *r*= 0.52 (P<0.001) with the stair climb power. Climb power in wattage per kg is calculated by the following formula: body weight(kg) x 9.81 x (height stairs (m)/time(s)).

  Sit-to-Stand test is a recognized Senior Fitness Test and used to assess an individual's lower-body strength.[93] This is done by having the individual sit on a chair and attempt to stand as many times in a maximum of 30 seconds. [949596]

  The sit-to-stand test requires a minimum amount of instrumentation. The necessary equipment includes the use of a stopwatch and a standard armless chair. The back of the chair should be placed against a wall to maintain stability and prevention of slipping.[97] Patients are encouraged to have their arms crossed on their chest during the test to avoid the use of the upper limbs. Patients are instructed to rise from the chair to a full stand on the signal "go" and then return to a fully seated position. The individual is allowed to have at most two practice trials and a demonstration should be given. The demonstration should be done slowly at first to show proper form and another demonstration should be given at a faster pace to show that the objective of the test is to do as many sit to stands one can do in the given amount of time.[98]

- The indirect 1 repetition measures are used to dose the training and will be administered at baseline, on the day before surgery, in the week after discharge from surgery and at 4 and 8 weeks after surgery to assess the impact of the intervention throughout the perioperative period. Muscle groups tested by 1-RM measurements are [99] The 1RM is calculated by the Brzycki formula: 1RM=W*36/(37-r) (w=weight, r=repetitions).[100]

- Nutritional status, including body composition, will be assessed at baseline, after completion of the program and 4 and 8 weeks postoperatively by using the following tools:

  - The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) screening tool will be used to identify malnutrition. This is an internationally validated instrument and preferred screening method to identify malnutrition in oncologic patients. [101,102,103,104,105] A three-day food diary filled in by patients is used to assess protein and calorie intake [108]. The energy requirements of the patient are calculated by the Harris-Benedict formula by Rosa.[106,107] Håkonsen et al recommended the PG-SGA as a nutritional assessment tool in colorectal cancer patients in combination with other parameters.[108] The PG-SGA consists of two parts: 1) the first part is the Patient Generated Subjective Global Assessment Short Form (PG-SGA SF) which includes a brief questionnaire addressing current weight, weight history, acute weight changes, changes in food intake over the past month, occurrence of nutrition impact symptoms experienced over the previous 2 weeks and changes in physical activities and functions over the previous month. The PG-SGA SF will be completed by patients themselves and generates a score for nutrition risk. The PG-SGA SF is a widely validated malnutrition screening tool in cancer patients.[109] 2) The second part will be completed by the dietician and includes a physical examination, where fat and muscle stores an fluid status are assessed, and assessment of the disease/ condition and metabolic demand. The global PG-SGA generates a subjective category rating for nutritional status: well-nourished (PG-SGA A), suspected malnutrition or moderate malnutrition (PG-SGA B), or severe malnutrition (PG-SGA C). It also provides a numeric score used for triaging (nutritional) intervention, i.e. to indicate the need for a calorie enriched diet.

  - Anthropometry. For a first impression of body composition and function, a minimal set of anthropometric measurements are performed. Body weight, length, triceps skinfold, hand grip strength and circumferences of wrist, waist and upper arm are measured. With these measurements, body frame can be determined, and Body Mass Index (body weight (kg)/ (length)^2), and muscle- and fat surface area can be calculated. When compared with reference values, one can assess (change in) body weight, (subcutaneous) fat mass, (upper limb) muscle mass and muscle strength, taking into account patients' body frame (S, M, L).[110] Measurements will be carried out according to the Anthropometry Procedures Manual of the National Health And Nutrition Survey.[111]

- Body Mass Index will be calculated with the equation body weight (kg)/ body length (cm)^2. According to the following classification patients' body weight status will be categorized:

  BMI < 18,5 (18-65 years old), BMI < 20 (> 65 years old), BMI < 21 (COPD) underweight
  BMI 18,5/20 or 21(dependent of age/COPD) -24,9 normal weight
  BMI 25 (18-65 years old), BMI 27 (> 65 years old) -30 overweight
  BMI > 30 obesity or severe overweight

- Percentage of body weight loss in the previous 1 and 6 months will be calculated based on the measurement of current body weight and anamnestic required body weight of 1 month or 6 months ago.

- Food diary & 24-hour recall

  In the week before start of the training program and in the last week prior to surgery, a three-day food diary will be filled in by the patient and assessed by a registered dietician, to obtain information about patients' food intake. During hospitalization the period (days) of being sober until commencement of oral intake is recorded. At the 5th day of hospital admission, a registered dietician will perform a 24-h recall, to estimate energy and protein intake of the day before and to determine caloric or protein shortage. The energy requirements of the patient are calculated by the Harris-Benedict formula by Roza.[112, 113]

  - Estimated energy requirements

  Energy requirements will be estimated using the revised resting energy expenditure (REE) predictive equation of Harris and Benedict,[113] adjusted for relevant stress and activity factors (1,3-1,5).
  In a validation study of predictive equations for resting energy expenditure in adult in- and outpatients, Weijs et al[114] showed that the revised Harris and Benedict was one of the best predictive equations, also for underweight patients. Total energy expenditure will be calculated by increasing estimated REE with 30-50%, dependent on stress and activity factors.[57]

  - Estimated protein requirements

  Due to anabolic resistance in elderly patients, higher dietary protein intake is required to obtain positive protein balance and to maintain or increase muscle mass. Also, inflammatory disease such as cancer and physical (strength) training elevate protein requirements. The required amount of protein will be estimated according to the following calculations:
  - 1.5-1.8 gram protein/ kg body weight*, daily**
  - 0.4 gram isolated whey protein/ kg body weight*, within 1 h-post exercise and before sleep

  *In case of underweight, protein requirements are underestimated since the body contains more protein/ kg body weight when compared to normal body weight. Opposing, in overweight subjects, protein requirements are overestimated when actual body weight is used in this equation. Therefore, in over- and underweight patients, adjusted body weights will be used in this equation, according to current guidelines for cancer patients.[57]

BMI	Correction
< 20	Adjustment of body weight to a body weight in accordance with a BMI of 20 protein recommendation (grams) x length (m)^2 x 20
20-27	Actual body weight
>27	Adjustment of body weight to a body weight in accordance with a BMI of 27 protein recommendation (grams) x length (m)^2 x 27

  Patients are recommended to use dietary proteins in boluses of 20 grams (70+ years: 25 grams)- 30 grams of dietary protein per meal, since this may increase protein synthesis.
  ** The safe upper limit for dietary protein intake is unknown. Protein recommendations for high intensity strength training go up to 2.0 gram/ kg body weight.

- Health-related quality of life (HRQL) as measured by the acute (1 week recall period) RAND health survey (19) and the EORTC QLQ-C30 for cancer patients and EORTC QLQ-CR29 specifically for colorectal cancer patients. The RAND is the most widely used HRQL measure and has been validated for surgical population (20). It incorporates behavioral functioning, subjective well-being and perceptions of health by assessing, on a 0 to 100 scale, eight health concepts: (1) Physical function (PF) -limitations in physical activities due to health problems; (2) Role physical (RP)-limitations in role activities due to physical health problems; (3) Role emotional (RE) -limitations in usual role activities due

to emotional problems; (4) Social functioning (SF) –limitations in social activities due to health problems; (5) Bodily pain (BP)-pain; (6) General health (GH) -general health perceptions; (7) Vitality (VT) -energy and fatigue; and (8) Mental health (MH) -general mental health. Two summary scores have been developed: the Physical Component Summary (PCS) and the Mental Component Summary (MCS)), standardized to have a mean of 50 and a standard deviation of 10. A higher score on the RAND sub-scales or component summary measures indicates a better quality of life. A change of as little as two units on the PCS has been shown to be the minimum clinically meaningful change; 5 points is often targeted by medical intervention studies, though surgical interventions can have an impact as large as 10 points. The RAND and EORTC QLQ-CR29 and EORTC QLQ-C30 will be measured at baseline, before surgery, 4 weeks, 8 weeks and 1 year after surgery.

- The vulnerability of older patients will be measured by two different scores, the fried frailty score and the G8 score. The Fried Frailty Score will be looked at (baseline) to determine whether the patient can be classified as frail based on five different categories such as weight loss, weakness through hand grip, endurance, slowness and activity level.[115] The G8 score is an instrument based on 8 different items to indentify a geriatric risk profile in patients and has a strong prognostic value for deterioration and survival.[116] It has a high sensitivity and negative predictive value to asses the fragility of older patients with cancer who will go for elective abdominal surgery and will be measured at the start of the study.[117]

- Physical activity level will be measured through an activity questionnaire derived from the Community Health Activities Model Program for Seniors (CHAMPS) questionnaire.[118] This questionnaire is a self-reported measure of physical activity, comprising 18 activities evaluated according to the total number of hours done during an average week. Physical activity will be measured at baseline, before surgery, and at 4 and 8 weeks after surgery. More objective levels of physical activity are assessed using an accelerometer, a small and lightweight device, which detects accelerations. Patients in both the intervention and control group will wear the accelerometer for 4 weeks. Although accelerometers may underestimate some activities, such as cycling and water activities, it is recognized as a reasonably valid tool to objectively assess physical activity.[119,120,121,122] Accelerations are converted into activity counts per minute, indicating the level of physical activity.

- Depression and anxiety will be assessed by the GAD-7 and PHQ-9 questionnaires at baseline, before surgery, and at 4 and 8 weeks after surgery. The GAD-7 is a valid and efficient tool for screening for generalized anxiety disorder (GAD) and assessing its severity in clinical practice and research.[123] The PHQ-9 including nine questions, is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria on which the diagnosis of DSM-TV depressive disorders is based.[124]

- Compliance with the interventions is assessed by self-report, and attendance and exercise logs filled in by either the physical therapists or kinesiologist and psychologist (e.g. observed attendance at and compliance with the exercise). Non-responders and dropouts receive a short questionnaire to assess the reason for non-participation or dropping out of the study. Satisfaction with intervention after completion of the intervention programs, patients are asked to complete a brief questionnaire addressing the perceived efficacy of and satisfaction with the program, whether they would suggest any changes to the program and if they would recommend it to other patients undergoing similar treatments.

- Costs of the exercise programs, data on health care costs, patient and family costs and costs of production losses are collected using monthly cost diaries measured on a three-monthly basis during the entire follow up period. Health care costs include the costs of oncological care, general practice care and physiotherapy, additional visits to other health care providers, prescription of medication, professional home care and hospitalization. Patient and family costs include out-of-pocket expenses such as travel expenses and costs for paid and unpaid help. Costs related to production losses include work absenteeism for patients (or parents) with paid jobs and days of inactivity for patients (or parents) without a paid job.

Patients will return to the hospital at 4 and 8 weeks to see the either the sport physician or physiotherapist/kinesiologist, as well to collect the postoperative data. Questionnaires for PROMs will be additionally performed 1 year post surgery. We will also measure surgical reinterventions, chemotherapy, hospital visits and mortality1 year postoperatively.

8.4 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.

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable.

8.5 Replacement of individual subjects after withdrawal

Patients will not be replaced after withdrawal.

8.6 Follow-up of subjects withdrawn from treatment

Regular follow up will be performed for all patients.

8.7 Premature termination of the study

In case of significantly increased incidence of serious side-effects in patients within the intervention group, the study will be ended. Otherwise inclusion will continue. Serious side effects might be cardiac arrhythmias or other exercise related problems during the VO2 maximal intensity exercise tests.

9. SAFETY REPORTING

9.1 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 jeopardize 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.

9.2 AEs, SAEs and SUSARs

9.2.1 Adverse events (AEs)

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

9.2.2 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 hospitalization or prolongation of existing inpatients' hospitalization;
- 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.

Since the participants in the study are operated for colorectal cancer AEs and SAEs are to be expected in both study arms. The primary endpoint of the study is the complication ratio expressed as the Comprehensive Complication Index. All SAEs will be discussed with among the surgeons in each participating hospital.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.
SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

9.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable.

9.3 Annual safety report

Not applicable.

9.4 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 until the end of the study, as defined in the protocol.

9.5 Data Safety Monitoring Board (DSMB) / Safety Committee

An independent Data Safety Monitoring Board (DSMB) will be asked to monitor the progress of the study and the safety of its participants. The DSMB will include: Dr. B van den Heuvel MD PhD, surgeon, Jeroen Bosch Hospital, 's Hertogenbosch, Dr. S. Houterman, epidemiologist, Dr. T Backhuijs, sports physician, Máxima Medical Center, Eindhoven –Veldhoven. The DSMB will meet as required to review any expected

adverse events and may ask to review outcomes or other data that may have an impact on the trial. **Every 10 SAEs will be reported to the DSMB by the sponsor.**

The advice of the DSMB will only be sent to the sponsor of the study. The sponsor will decide if the advice of the DSMB will be implemented. And will subsequently update the reviewing METC on this advice including a note to substantiate why (part of) the advice of the DSMB will not be followed).

STATISTICAL ANALYSIS

Data will be analyzed according to a detailed statistical analysis plan, which will be available before the final data freeze to allow for corrections based on data checks and database cleaning

9.6 Primary study parameter(s)

Data will be analyzed on an intention-to-treat basis. In addition, a per-protocol analysis will be performed.

The first primary outcome is postoperative complications, as scored by the Comprehensive Complication Index score (CCI).[125] Data will be collected as a continuous variable and calculated through the sum of morbidity and mortality presented on the Clavien Dindo classification.[126] CCI score will be calculated at the 30 day follow up.
CCI will be described as mean plus standard deviation (SD). However since we expect CCI to be right skewed (i.e. tail to the right) we will also describe CCI as median plus interquartile range (IQR) and percentage above 20.
We will visually check the distribution of the CCI data using histograms and calculating skewness and kurtosis. If necessary and if possible the data will be normalized by applying (normal) logarithmic transformation.
To test the hypothesis (H0) that the study arms result in similar CCI's (i.e. prehabilitation does not prevent postoperative complications), we will use the student T-test if data follow a normal distribution, a Mann-Whitney U if data do not follow a normal distribution or statistical methods that take into account a possible zero-inflated nature of the data.

The second primary/confirmatory outcome is the patients' functional capacity, as measured by the six-minute walk test (6MWT). The 6MWT is a continuous variable and calculated at baseline (inclusion to the study), a few days before surgery and 4 and 8 weeks after surgery.
Data will be described by means plus SD per time point. To accommodate the repeated measurements within individuals we will use a generalized linear mixed model to statistically test the hypothesis of both study arms being equal regarding functional capacity over time.

9.7 Secondary study parameter(s)

Secondary outcomes will include cardiopulmonary exercise testing (CPET), Health-related quality of life (HRQL), Sit-to-Stand test, hand grip strength, body composition, stair climb test, Physical activity level measured through an activity questionnaire, derived from the Community Health Activities Model Program for Seniors (CHAMPS), depression and anxiety assessed by GAD-7 and PHQ-9, nutritional status, compliance, length of hospital stay, and costs.
All secondary outcomes will be described as means plus SD or median plus IQR where data are continuous and normally respectively non-normally distributed measures, per time point. Categorical parameters will be described as number plus percentage per time point. Statistical methods will include t-test and Mann-Whitney U test for continuous normally respectively non-normally distributed parameters at a single time-point post-operatively. Categorical outcomes will be analyzed by using Chi-square tests or (logistic, ordinal or nominal, depending on the definition of the parameter) regression analysis for single time points.
To accommodate the repeated nature of the data and describe time effects, we will apply a generalized linear mixed model using the appropriate link-function (i.e. linear, poisson, logistic etc.).

9.8 Other study parameters

Not applicable.

9.9 Interim analysis (if applicable)

Due to limited clinical data and resulting uncertainty regarding effect size of the primary endpoint – CCI - an interim analysis will be performed. The interim analysis is planned if half of the intended number of subjects have completed the 8 week assessment (i.e. timing of the primary endpoint assessment). The intention of the interim analysis is to terminate the study if there is a statistical significant difference between study arms at an alpha of 0.0054 (O'Brien-Fleming stopping rule) or if the recalculated sample size is deemed unattainable (i.e. larger than 1000 patients) or if the difference is not clinically relevant (<5 percent)

The sample size at the time of interim analysis will be sufficient to still show clinically relevant statistical differences regarding the second primary endpoint (i.e. 6MWT).

The interim analysis will be performed by the epidemiologist of the MMC, who is not a member of the DSMB. Early termination of the study will be decided upon by the DSMB.

To account for the alpha spending upon interim analysis (the final alpha will be 0.049), the sample size needs a minor adjustment from 708 to 713 patients. If the sample size recalculation in the interim analysis implies adjustment of the required sample size, this will be processed through an amendment to the protocol.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki55 and in accordance with the Medical Research Involving Human Subjects Act (WMO).

10.2 Recruitment and consent

Due to the fact that Dutch guidelines request that a colorectal cancer patient should be operated within 5 weeks after the positive result from the lab, the timelines for recruitment and informed consent are short to allow enough time for training. Patients will be given information about the study via the research subject information leaflet by the gastroenterologist if after colonoscopy the patient is highly suspected for having colon cancer (95% certainty). After confirmation of cancer diagnosis, his/her permission is requested to be contacted about the study by the researcher. The researcher will contact the patient to answer any questions that he/she might have and ask if the patient is willing to participate in the trial. The patient information letter and informed consent are provided in the attachments of the study dossier. The right of a patient to refuse participation without giving reasons will be respected. The patient will remain free to withdraw at any time from the study without consequences for further treatment.. In case of a positive answer, a first meeting will be scheduled at the sports physician. The sport physician will obtain the written informed consent prior to the first baseline measurements. During the first baseline measurements the patient will be randomized using Research Manager. After the measurements, the patient is informed about the result of the randomization. Patients are informed that their data is coded, and will be stored for 15 years before destruction.
The independent doctor available for patients is dr. Vreugdenhil (+31408885320)

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable.

10.4 Benefits and risks assessment, group relatedness

Patients in the prehabilitation group might benefit since they will be actively working on their physical and nutritional health status. No minors and incapacitated subjects will be included in the study, due to the impossibility to perform all exercises and fulfill all questionnaires. Side effects might be cardiac arrhythmias or other exercise related problems during the VO2 maximal intensity exercise tests. Exercise training is not expected to cause any risk to patients. However, since patients are thoroughly screened, we expect to find more pre-existing cardio-pulmonary conditions, for which patients will be referred to either a pulmonologist or cardiologist. The amount of tests might be perceived as a burden for the patients in both groups, as well as the amount of hospital visits for the prehabilitation group.

10.5 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.

10.6 Incentives (if applicable)

Participants will not receive a standard financial compensation for participation as an incentive. However, they will receive travel compensation of 10 euro per visit to the hospital.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be managed by a online data management system 'research manager'. Patients receive an unique study number, generated by the data management system. Study number is linked to patient details and stored in a secured file with password. Only the researcher and research nurse have access to this file. No human material will be collected.

11.2 Monitoring and Quality Assurance

Monitoring will be performed via a risk-based approach, as recommended by the FDA. Although monitoring is legally not required for this study, the sponsor (MMC) has decided to perform monitoring for all studies that fall under the scope of the WMO-act. Since this study has a minimal risk, monitoring should be performed annually and will partially be done centralized. Centralized monitoring is a remote evaluation carried out by sponsor personnel or representatives (e.g., clinical monitors, data management personnel, or statisticians) at a location other than the sites at which the clinical investigation is being conducted. Centralized monitoring processes can provide many of the capabilities of on-site monitoring as well as additional capabilities.

11.3 Amendments

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

11.4 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.

11.5 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.

11.6 Public disclosure and publication policy

The trial is registered in the trial register under code NTR 5947

12. STRUCTURED RISK ANALYSIS

12.1 Potential issues of concern

Not applicable.

12.2 Synthesis

Not applicable.

13. APPENDICES

Appendix I

Table 1. Prehabilitation randomized controlled trial scheme

	Preoperative			**Operation**	**Postoperative**		
Weeks	**-5**	**-4**	**-1**	**0**	**4**	**8**	**52**
	Before start	**Baseline**	**Preoperative**	**Surgery**	**30 day follow up**	**8 weeks follow up**	**1 year follow up**
Gastroenterologist	Inform patient	-	-	-	-	-	-
Sport physician	-	Informed consent VO2max Anaerobic threshold Exercise-ECG	VO2max Anaerobic threshold Exercise-ECG	-	VO2max Anaerobic threshold Exercise-ECG	-	-
Physiotherapist	-	6MWT Stair climb test Sit-to-stand test 1-RM test Activity questionnaire (derived from CHAMPS)	6MWT Stair climb test Sit-to-stand test 1-RM test Activity questionnaire	-	6MWT Stair climb test Sit-to-stand test 1-RM test Activity questionnaire	6MWT Stair climb test Sit-to-stand test 1-RM test Activity questionnaire	-
Dietician		Food diary (3 days) Height, weight Weight loss %* Wrist/abdominal/ Upper arm circumference Skinfold measurements Hand grip strength PG-SGA	Food diary (3 days) Height, weight Weight loss %* Wrist/abdominal/ Upper arm circumference Skinfold measurements Hand grip strength PG-SGA	-			-
Psychologist	-	Intake when indicated (details in protocol)	-	-	-	-	-
Anesthesiologist	-	-	Preoperative screening**	ERAS**	-	-	-
Surgeon	-	-	ERAS**	-	-	-	-
Surgical resident	-	-	-	-	Outpatient data	-	-
Researcher/ Case manager	Inclusion patient	Intake Coping with anxiety HRQoL GAD-7 PHQ-9 Fried Frailty Score G8 score	HRQoL GAD-7 PHQ-9 Program evaluation & health costs (brief)	-	Weight and weight loss %* Hand grip strength PG-SGA score 30-day morbidity and mortality HRQoL GAD-7 PHQ-9 Program evaluation Health costs	Weight and weight loss %* Hand grip strength PG-SGA HRQoL GAD7 PHQ-9	Mortality Activity questionnaire Health and life style HRQoL GAD-7 PHQ-9

Appendix II: Exercise training program

Detailed description of exercise training for the prehabilitation group.

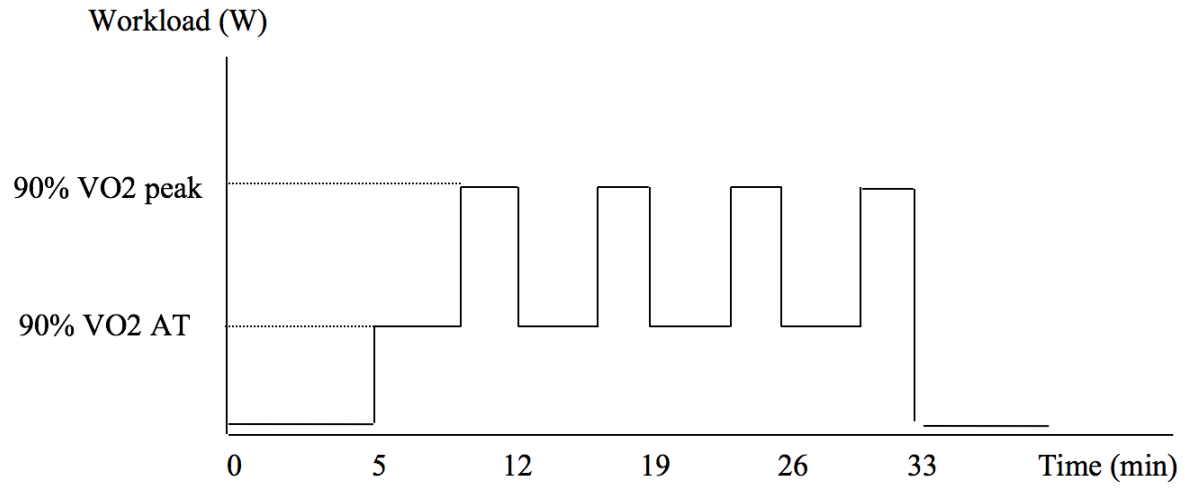
[1] Endurance training, based on CPET data: VO2peak/AT

[2] Resistance training, 1RM

[3] Homework

Endurance training, based on CPET data (VO2peak / AT)

- HIT = High intensity individualized interval training
  - This supervised training will be done three times a week.
  - The interval training duration is 28 minutes and performed with 4 intervals of Moderate intensity (3 minutes) and 4 intervals of High intensity (4 minutes). If the patient is unable to complete the high-intensity bout, the intensity is reduced by ten percent. The intensity is reduced further – in steps of ten percent – until the moderate activity level is performed if patients still cannot complete the bout. The remaining time of the bout will be continued at this level, after which the program will be completed as intended.
  - The workload is dosed at a percentage of VO2peak. High intensity is considered 90% of VO2peak. Moderate intensity 90% of VO2 AT.
  - This interval training aims to reach levels of Borg 15-17 and >85% of the maximum heart rate (determined at the CPET), as long as the patient could effort the exercise.
  - Exercise may be performed on a bicycle, a rower, a treadmill and/or on other aerobic exercise machines.



Resistance training, 1RM

- This supervised training will be done three times a week.
- Strength training will be the same concept for all patients irrespective of VO2-peak.
- The 1RM will be determined at baseline using: lateral pull down, leg press, chest press and abdominal crunch. The strength exercises are performed according to: 2 seconds of concentric strength and 2 seconds of eccentric strength. The 1RM is calculated by the Brzycki formula:
  - *1RM= W*36/(37 –r)*
  - *W* = weight in kilograms
  - *r* = repetitions
- The strength training consists of two series of 10 repetitions of six exercises: leg press, chest press, abdominal crunch, lat pull down, low row and step up.
  - In week 1 using 65% of calculated 1RM (at baseline)
  - In week 2 using 70% of calculated 1RM
  - In week 3 using 75% of calculated 1RM
  - In week 4 using 75% of calculated 1RM
- The last bout with 10 repetitions needs to be attainable. If this is not the case in the next session dosing will be 5-10% lower. If in the last bout it appears that exercises are to low (≥15 repetitions will be achieved), in the next sessions dosing will be 5-10% higher.

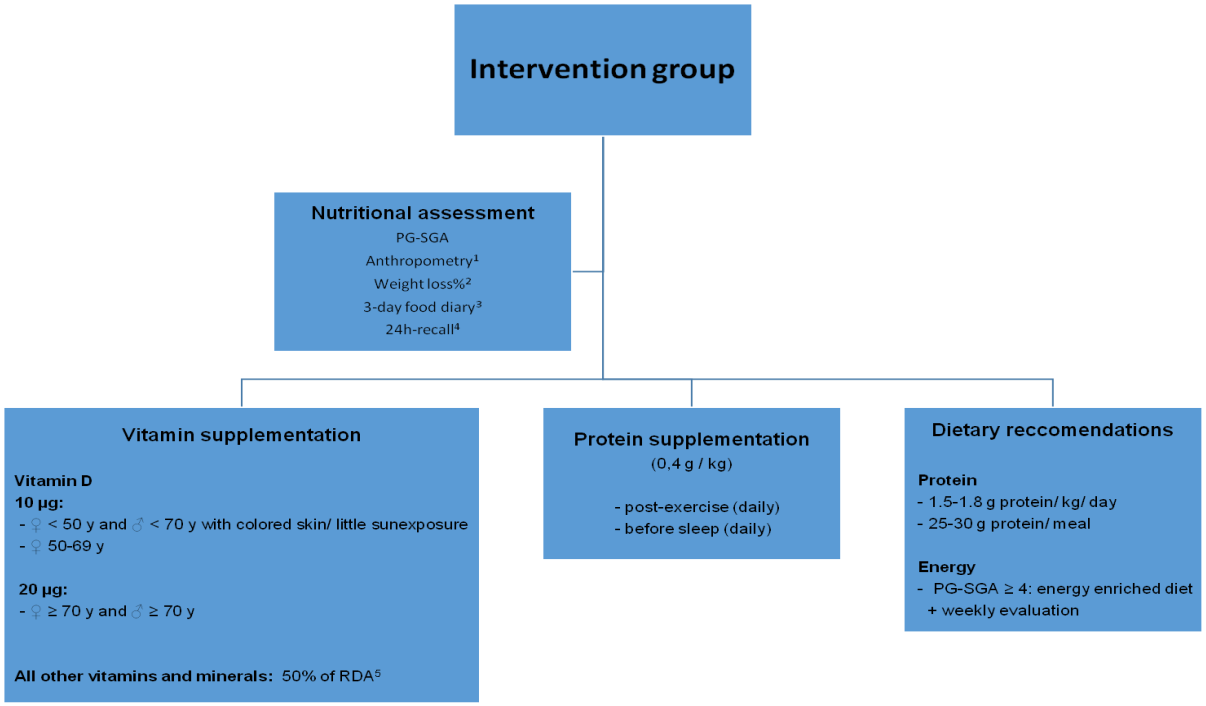
Homework/Counseling:

- The homework will be done at the days without supervised training, this will be a total of four days a week.
- Patients are instructed to aim at 60 minutes walking and/or cycling a day, but at least 30 minutes a day. If possible, patients can do more than 60 minutes of walking or cycling every day.
- Because of the low exercise capacity it is advised to walk/cycle 2-3 times a day for periods of 10-20 minutes.
- Also an electric bicycle, a stationary bicycle and/or a walking aid (walker) may be necessary.

Rest:

- Patients are instructed to take care of recovery and adequate rest and sleep.
- From 3 days before surgery no high intensive interval training and strength training are done. The patient will continue with the homework/counseling (walking/cycling every day) and the dietary supplements.

Appendix III: Nutrition



[1]Height, weight, wrist circumference, abdominal circumference, upper arm circumference, triceps skinfold, hand grip strength. The following can be calculated: BMI, body frame, (upper limb) muscle mass, (subcutaneous) fat mass.

[2]% weight loss in previous month and previous 6 months

[3]Before start prehabilitation, week before surgery, 8 weeks post-surgery

[4]On 4th day of hospital admission (if still in hospital)

[5]Recommended Daily Allowance

Appendix IV: Definitions of complications used after bowel surgery

INTRAOPERATIVE COMPLICATIONS[1]

- *Clinically significant hemorrhage:* intraoperative bleeding requiring transfusion of packed red blood cells (PRBC) during surgery or within 24 hours after surgery
- *Bowel injury:* injury of the small or large bowel requiring intraoperative repair or additional resection.
- *Urinary tract injury:* injury of the ureter or bladder requiring intraoperative repair
- *Vascular injury:* injury of any major vessel (e.g. iliac artery or vein) requiring intraoperative repair
- *Cardiac or respiratory complications:* any cardiovascular (e.g. cardiac arrhythmia, myocardial infarction) or respiratory (e.g. pneumothorax) complication occurring during surgery.
- *Aspiration of gastric content:* intraoperative pulmonary aspiration of gastric content
- *Other:* any intraoperative injury to other viscera (e.g. spleen, vagina)

POSTOPERATIVE COMPLICATIONS

MEDICAL

Cardiovascular

- *Heart failure:* clinical or radiological signs of congestive heart failure and specific treatment initiated.[2]
- *Acute myocardial infarction:* increase in cardiac biomarker values or characteristic ECG changes or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality.[3]
- *Cardiac arrhythmia:* ECG diagnosis of new arrhythmia requiring at least a pharmacologic intervention.[4]
- *Cardiac arrest:* cardiopulmonary resuscitation performed.
- *Deep vein thrombosis:* radiological confirmation of deep vein thrombosis or anticoagulation started due to clinical findings.
- *Pulmonary embolism:* radiological evidence of pulmonary embolism.
- *Cerebrovascular accident:* new focal or global neurologic deficit of cerebrovascular cause that persists beyond 24 h or is interrupted by death within 24 h.[5]

Respiratory

- *Pneumonia:* Hospital acquired pneumonia, defined as presence of lung infiltrate at chest x-ray accompanied with signs of infection and initiation of antibiotic treatment. [6]
- *Lobar atelectasis:* radiological finding of at least one lobar collapse.[4]
- *Pleural fluid:* pleural effusion requiring drainage of the pleural cavity.
- *Respiratory failure:* delayed extubation > 24 hours after primary surgery, or reintubation at any time for ventilatory support.[4]
- *Pulmonary edema:* clinical signs and radiological confirmation.[7]

Other medical

- *Acute Kidney Injury:* increase in serum creatinine ×2 from baseline or reduction of glomerular filtration rate greater than 50%.[8]
- *Urinary retention:* Reinsertion of indwelling urinary catheter after removal attempt or patient discharged with urinary drainage (excluding patients with permanent indwelling urinary catheter).
- *Anemia:* low serum hemoglobin requiring transfusion of PRBC, unrelated to any identified source of bleeding.
- *Hepatic dysfunction:* Increased serum bilirubin concentration > 34 µmol/l (2 mg/dl) compared to preoperative value AND elevated liver enzymes AND has NOT undergone a pancreaticobiliary procedure.[4]
- *Acute Pancreatitis:* diagnosis requires 2 of the following: upper abdominal pain of acute onset often radiating through to the back; increase in serum amylase or lypase (x3 normal value); cross- sectional abdominal imaging consistent with acute pancreatitis.[9]
- *Other gastrointestinal complications:* any other complication of the gastrointestinal tract requiring treatment (e.g. blood per rectum, diarrhea, high stoma output).
- *Neurological complications:* any neurological complication excluding cerebrovascular events or anesthesia-related injuries (e.g. epileptic seizure)

- *Psychiatric complications:* new psychiatric symptoms including delirium and depression, requiring pharmacological treatment.

INFECTIOUS

- *UTI:* upper or lower urinary symptoms and urine culture with no more than two species of organisms, at least one of which is a bacteria of $\geq 10^5$ CFU/ml.[10]
- *Wound infection:* Purulent drainage, with or without positive culture, from the superficial incision or any sign or symptom of infection (e.g. pain or tenderness, localized swelling, redness) and superficial incision is deliberately opened by the surgeon or attending physician. Not included if part of intra-peritoneal abscess.[11]
- *Intra- or retroperitoneal abscess:* Radiologic finding of deep collection of pus associated with systemic signs of infection or finding during reoperation.
- *Sepsis*: at least two SIRS criteria positive and a documented or suspected infection. SIRS criteria are the following: Temperature < 36 or >38 ºC; heart rate >90 beats per minute, respiratory frequency >20 breath per minute, leukocytosis (WBC>12) or leukopenia (WBC<4) AND documented or suspected infection.[12]
- *Other infectious complications:* any other documented infectious complication (e.g. Clostridium difficile colitis).

SURGICAL

- *Anastomotic leak: d*ocumentation at reoperation OR documentation by imaging technique (e.g. radiologically, endoscopically) of leakage from the surgical connection between the two bowel ends into the abdomen or pelvis with either spillage and/or fluid collection around the anastomotic site or extravasation through a wound, drain site, or anus.[13] In the case of rectal surgery, a pelvic abscess close to the anastomosis is also considered as anastomotic leakage.[14]
- *Bowel perforation:* documentation at reoperation OR radiologically of perforation of small or large bowel.[7]
- *Mechanical bowel obstruction:* documentation at reoperation OR radiologically of mechanical small or large bowel obstruction.
- *Wound dehiscence:* separation of the abdominal wall muscle fascia large enough to necessitate operative closure of the wound OR incisional hernia diagnosed after primary discharge.[7]
- *Bleeding:* any postoperative bleeding (e.g. intra-abdominal, gastrointestinal) requiring transfusion of at least 2 PRBC after surgery.[15]
- *Ileus (primary postoperative ileus):* abdominal distention OR vomiting associated with intolerance of solid food intake or inability to pass gas or stool beyond POD3 (target day for discharge), unrelated to any other ongoing complication.
- *Other surgical complications:* any other surgical complication necessitating treatment or delaying discharge (e.g. abdominal wall hematoma).

ANESTHESIA-RELATED

- *Post-dural puncture headache:* persistent headache requiring immobilization, related to puncture of the dura mater during epidural catheter placement
- *Epidural hematoma or abscess:* radiologically confirmed epidural hematoma or abscess
- *Other anesthesia-related complications:* any other anesthesia-related complication occurring after surgery (e.g. peripheral nerve injuries).

SYMPTOMS DELAYING DISCHARGE

- *Pain:* uncontrolled pain requiring prolonged treatment delaying discharge, unrelated to any other complication.

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