BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-072805
Article Type:	Protocol
Date Submitted by the Author:	14-Feb-2023
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Keywords:	Renal transplantation < NEPHROLOGY, NUTRITION & DIETETICS, Rehabilitation medicine < INTERNAL MEDICINE, MENTAL HEALTH, Quality of Life

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study: protocol for a hybrid type I, mixed method, randomized controlled trial

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ABSTRACT

Introduction: Kidney transplant candidates (KTCs) need to be in optimal physical and psychological condition to handle the stress of the upcoming transplant surgery and recovery after transplantation. However, the functional capacity of KTCs is often compromised due to factors relating to chronic kidney disease, including comorbidities and dialysis, which can be characterized as frailty. Prehabilitation, the enhancement of a person's functional capacity in order to improve their ability to withstand future stressors, may be an effective intervention to improve the health status of KTCs. The PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study aims to examine the effectiveness of a multi-modal prehabilitation program on the health status of KTCs, and to explore the potential of implementation of prehabilitation in daily clinical practice.

Methods and analysis: The PreCareTx study is a single centre, effectiveness-implementation hybrid type I study design, comprised of a randomized controlled trial and a mixed-methods study. Adult patients who are currently on the transplant waiting list or are waitlisted during the study period, will be randomly assigned to either prehabilitation (n=64) or care as usual (n=64) groups. The prehabilitation group will undergo a 12-week tailored prehabilitation program consisting of physical and/or nutritional and/or psychosocial interventions depending on the participant's deficits. This program will be followed by a twelve-week consolidation program in order to enhance the incorporation of the interventions into daily life. The primary endpoint of this study is a change in frailty status as a proxy for health status. Secondary endpoints include changes in physical fitness, nutritional status, psychological well-being, quality of life and clinical outcomes. Tertiary endpoints include the feasibility and acceptability of the prehabilitation program, and the barriers and facilitators for further implementation.

Ethics and dissemination: Medical ethical approval was granted by the Medical Ethics Committee Groningen, The Netherlands (M22.421). Trial registration number: NCT05489432, ClinicalTrials.gov.

Strengths and limitations of this study

Strengths

- The intervention was developed in co-creation with kidney transplant candidates and recipients, their significant others and healthcare providers involved in kidney transplant care. This goal-directed prehabilitation program will be tailored to the needs and possibilities of the patient so that it can be incorporated into daily life.
- A randomized controlled trial will provide a high-quality assessment of the effect of a multimodal, tailor-made prehabilitation program on frailty and other important patient-centred outcomes regarding physical fitness, nutritional status and psychosocial well-being.
- A mixed methods study will provide insight into the feasibility and acceptability of prehabilitation in a real-world setting by analysing the barriers and facilitators associated with this intervention.

Limitations

- This single-centre study only includes kidney transplant candidates.
- The study was not double-blinded due to the nature of the intervention.

INTRODUCTION

Kidney transplant candidates (KTCs) may have a compromised health status due to disease progression, comorbidities, and the adverse effects of dialysis. This may lead to impaired physical fitness, lower quality of life, and an increased risk of developing psychological problems. (1, 2, 3, 4, 5) Poor health status is related to a low level of physical activity, eliciting a cycle of deteriorating physical fitness in which multiple factors are involved, including muscle wasting, malnutrition, inflammation, and fatigue. (4) Data from the TransplantLines Biobank & Cohort study (6) at our centre, the University Medical Center Groningen (UMCG), showed that of 424 KTCs, 87% had one or more problems related to physical or psychological fitness prior to transplantation. Regarding physical fitness, 55% of KTCs had problems related to decreased muscle strength and/or walking ability and 45% had a suboptimal nutritional status. Concerning psychological well-being, 36% showed high symptom levels of anxiety and/or depression. In addition, 58% of the KTCs experienced severe fatigue and 19% experienced moderate fatigue. These findings show that KTCs are a vulnerable patient population and exhibit signs of frailty. Frailty is a multidimensional syndrome and captures the multiple domains involved in the health status of KTCs. It is a physiological condition caused by declines across physical, cognitive and physiological reserves. (7, 8) Among KTCs, frailty is associated with an increased inflammatory state, hospitalizations and waitlist mortality. (9, 10, 11) It is estimated that one in six kidney transplant recipients is frail prior to transplantation. (12)

Studies have shown that physical fitness and psychological wellbeing can be improved by the means of prehabilitation. (13, 14, 15, 16, 17) Prehabilitation is an intervention aimed at optimizing the patient's overall fitness before an operation to enhance recovery after the surgery and improve outcomes. Prehabilitation may also be effective in improving the overall health status of KTCs prior to the kidney transplant. It focuses on implementing lifestyle changes in order to enable patients to withstand the stress of surgery, reduce the risk of post-operative

complications, unplanned readmissions, and to enhance recovery. (18) Prehabilitation comprises physical training, dietary management, and psychosocial interventions. (18) The waiting list period before the kidney transplant provides a window of opportunity to enhance the overall fitness of KTCs by prehabilitation. In the Netherlands, the duration of the waiting-list period ranges from less than 3 months for those who receive a kidney from a living donor to over three years in case of deceased donor kidney transplantation. Especially for the latter, the duration of the waiting-list period is unpredictable. By offering a prehabilitation program tailored to the needs and possibilities of KTCs prior to transplantation, patients may be more likely to adopt a sustainable, healthy lifestyle.

Studies have shown that prehabilitation during the waiting-list period in transplant candidates is feasible. (14, 17, 19, 20) Three studies showed that prehabilitation significantly improved physical activity, fatigue, walking time, and grip strength during the waitlist period in KTCs. (17, 19, 20) However, these studies had a small sample size, and the interventions were not provided in a multimodal approach. Therefore, the effectiveness of a multimodal tailored prehabilitation program in KTCs still needs to be determined.

The primary objective of this study is to measure the effect of a 12-week tailor-made multimodal prehabilitation program on changes in frailty status between baseline (T0) and T1. Furthermore, changes in physical functioning, nutritional status, psychological wellbeing, quality of life and clinical outcomes between T0 and T1 will be measured.

The secondary objectives are to determine the sustainability of the results regarding frailty status and changes in physical functioning, nutritional status, psychological wellbeing and quality of life at 6 months after the start of the study.

The tertiary objective of this study is to explore the potential for further implementation of prehabilitation in a daily clinical practice. This will be done by examining the feasibility and acceptability of the prehabilitation program and barriers and facilitators for further implementation.

METHODS AND ANALYSIS

Trial design

The PreCareTx study is a single centre, effectiveness-implementation hybrid type 1 study design, consisting of a randomized controlled trial and a mixed methods study. An overview of the study is given in Figure 1. The duration of the study will be three years, starting from January 2023. The study was reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement. (21) The study has been registered on ClinicalTrials.gov (NCT05489432).

Study setting

The intervention will be conducted in the KTCs' home environment, depending on their needs and preferences. Study visits will be conducted at the University Medical Center Groningen in The Netherlands at the following time points: baseline (T0), and at week 13 (T1) and week 26 (T2) after randomization.

Recruitment

Patients on the UMCG waiting list for kidney transplantation or waitlisted during the inclusion period, will be recruited by their treating physician and receive an information letter about the risks and benefits of the study. Written informed consent will be obtained from the patient. Patient recruitment will start in January 2023 and end in June 2025.

Eligibility criteria

In order to be eligible to participate in this study, potential participants must meet all the following inclusion criteria:

Prior to assessment:

1) Adult kidney transplant candidate (≥18 years).
2) Listed for kidney transplantation on the UMCG kidney transplant waiting list at the start of the study or waitlisted during the inclusion period (January 2023 – June 2025).

After assessment:

1) Having at least one problem regarding physical functioning, nutritional status, or psychological wellbeing.

The exclusion criteria prior to assessment include:

1) Inability to read and/or speak the Dutch language.
2) Combined organ transplantation (e.g., kidney+pancreas, kidney+liver).
3) In case of living donor kidney transplant: a transplantation planned within 3 months.
4) Involved in a lifestyle intervention study.

Participant screening & assessment

After informed consent, participants will be screened for problems regarding physical activity, nutritional status or psychological wellbeing in an assessment, comprised of questionnaires and physical tests. The details of the assessment are described in Table 1. Participants who present with one or more modifiable problem(s) will be eligible to take part in the intervention study.

Randomization and allocation concealment

All participants who present with at least one modifiable problem, as determined during the assessment at the baseline study visit, will be randomized to the intervention or control group on a 1:1 ratio using block randomization after stratification for sex and pre-emptive/non-pre-emptive transplantation. This study will not be blinded as it is not possible to blind the participant, or healthcare professionals involved in the intervention. Randomization will take place using ALEA (www.aleaclinical.eu). The randomization will be performed by an independent researcher who is not involved in screening, recruitment, clinical care, or data collection.

Intervention

The multi-modal, tailor-made program will focus on three domains: physical activity, nutritional advice, and psychosocial support. For each domain, interventions have been developed based on the behavioural change wheel (BCW) method. (15, 16) A context analysis was performed to gain insight into the problems KTCs face, and the factors (i.e., preferences, barriers, limitations and facilitating factors) that are important to them for the creation and implementation of a prehabilitation program. Two certified lifestyle coaches, a physiotherapist and a dietitian, will be involved in the intervention. The lifestyle coach, together with the participant and their significant other, will compose a personalized, goal-directed prehabilitation program that can be incorporated into the daily life of the participant. During the intervention, the lifestyle coach will provide (bi)weekly counselling sessions with the participant. Frequency of these visits will depend on the participant's preference. In these sessions, the progress of the participant, including their goals, facilitators and barriers, will be discussed.

Physical activity

The aim of the physical activity interventions will be to improve the strength and endurance of KTCs. The criteria of The Nederlandse Norm Gezond Bewegen (NNGB, in English: Dutch Healthy Physical Activity Guidelines), which includes: 1) performing activities that are moderately intense in nature for at least 30 minutes a day/five days per week, and 2) performing activities to increase muscle strength for 20 minutes a day/ 2-3 days a week, will serve as guidance. (22) The intervention will differ per participant depending on his/her baseline fitness level, preferences and whether or not they are on dialysis. (23) Figure 2 shows the various components which will be considered whilst creating the tailor-made intervention for each participant.

Nutritional advice

Nutritional interventions will focus on improving nutritional status and body composition by supporting participants to engage in healthy and sustainable dietary habits. If participants already receive guidance from a dietician in the context of regular care, the nutritional advice will be coordinated with his/her dietician. The intervention will be tailored to the nutritional problems and/or dietary restrictions of each individual participant and focus on optimizing and preventing shortages or imbalances of energy, protein and/or other nutrients for all participants.

Psychosocial support

Psychosocial interventions will consist of individual coaching by a certified lifestyle coach during (bi)weekly counselling sessions. The sessions will focus on the use of effective coping strategies, stress and energy management, and promoting social support. Significant others may take part in these sessions if the participant wishes that

they do. In addition, interventions aimed at relaxation such as sleep hygiene and relaxation interventions (e.g., progressive muscle relaxation techniques, visual and auditory stimulation, breathing techniques) will be offered. Participants with clinically relevant scores regarding anxiety (STAI6 ≥12) or depression (PHQ-9 ≥10) will be referred to a social worker at their local hospital for further evaluation, treatment and/or referral to a psychologist. (24, 25)

Control group

The control group will receive care as usual. Standard medical care for KTCs consists of a consult with a nephrologist and/or nurse practitioner at their local hospital every three months approximately. In addition, a consult with a dietician is scheduled if laboratory values are not consistent with expected results from dietary restrictions for CKD or upon demand of the KTC. Depending on the needs of the KTC a social worker can be consulted. Regarding measurements, the same time intervals will be used in between assessments. A study visit at the UMCG will be planned at week 13 (T1) and week 26 (T2) after randomization.

Withdrawal participant

Participants may always withdraw from the study, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants will be withdrawn if they get transplanted during the study.

If participants withdraw from the study prior to measurement point T1, new participants will be included to ensure sufficient power of the study. Participants who have withdrawn from the study after T1 but indicate that their data may be used in the follow-up studies (e.g., on the effect of prehabilitation on outcomes after transplantation) will be followed according to the specifications of the patient.

Outcome measurements

All outcome measurements are summarized in Table 1. The primary, secondary and clinical outcomes will be measured at three timepoints: T0 (baseline assessment), T1 (week 13) and T2 (week 26).

Primary outcome

The primary outcome will be change in frailty status between T0 and T1 as measured by the Tilburg Frailty Indicator (TFI). (26) In addition, the sustainability of the intervention will be examined by change in frailty status between T1 and T2. The TFI is a multidimensional, validated questionnaire for measuring frailty among community dwelling older adults. (26) It consists of 15 items reflecting the different components of frailty: physical frailty (8 items), psychological frailty (4 items) and social frailty (3 items). The total TFI score ranges between 0-15. A score ≥5 is used as a cut-off point for frailty.

Secondary outcomes

Secondary endpoints include changes in physical functioning, nutritional status, psychological well-being and quality of life. To measure these changes, a set of questionnaires will be filled out prior to the study visits (T0/T1/T2) in the UMCG using an online survey. Participants who prefer a pen-and-paper survey, will receive one via mail. Physical tests will be done during the study visit at the UMCG.

Physical functioning will be measured by two questionnaires and five performance tests.

- The Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH) will be used to gain insight into engagement in physical activities in one's daily life. (27)

- The Duke Activity Status Index (DASI) will be used to measure functional capacity. (28)
- An activity tracker will be used to measure the number of steps taken by the participant. Participants will be asked to wear the activity tracker for three days and note the steps per day in their food diary (see nutritional assessment).
- Handgrip strength will be assessed using the Jamar Hydraulic Hand Dynamometer (Patterson Medical JAMAR 5030J1, Warrenville, Canada). (29)
- Quadriceps and biceps strength will be measured with a hand-held dynamometer CITEC CT 3002/30 handheld dynamometer (Haren, The Netherlands). (30, 31)
- The Short Physical Performance Battery (SPPB) will be used to measure physical performance regarding balance, gait speed and leg muscle strength. (32) The SPPB consists of a balance test, a 4-meter walking test and the 5 Times Sit-To-Stand test (5TSTS).
- The steep ramp test (SRT) will be performed on an electronically braked cycle ergometer to measure one's aerobic capacity. During the SRT, the resistive load is accelerated in a fast schedule (25 W/10 sec) until exhaustion of the participant. (33)

Nutritional status will be assessed by a questionnaire, a food diary, and three body measurements.

- The Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) will be used to assess nutritional status across various domains: changes in body weight, changes in nutritional intake, symptoms which negatively influence intake, absorption and utilization of nutrients, and level of activities and function. (34)
- Participants will be asked to complete a food diary throughout consecutive three days, including one weekend day, to gather information on fat, protein, and energy intake.

- Body mass index (BMI) will be calculated as follows: weight (in kg) divided by height (m) squared (kg/m^2).
- Hip and waist circumference will be measured in centimetres to calculate a waist-hip ratio.
- Bio Impedance Analysis (BIA) will be performed to non-invasively measure body composition (e.g., lean tissue index, fat tissue index, extra cellular and intra cellular volume) by using the InBodyS10.

Psychosocial well-being will be measured by three questionnaires.

- Symptoms of anxiety will be measured using the short-form of the State-Trait Anxiety Inventory (STAI-6). (35)
- Symptoms of depression will be measured using the Patient Health Questionnaire-9 (PHQ-9). (36)
- Fatigue will be measured using one subscale of the Checklist Individual Strength: subjective fatigue (CIS8R). (36)

Health-Related Quality of Life

To assess health-related quality of life (HRQoL), the Short Form-36 (SF-36) health survey will be used. It is a 36-item, self-reported questionnaire that captures participants' perceptions of their own health and wellbeing. Based on the item scores, a physical component score (PCS) and a mental component score (MCS) will be calculated. (37, 38)

Clinical outcomes

Clinical outcomes, including waitlist mortality, delisting, and the number of hospital admissions, will be assessed by medical record review until time of transplantation and recorded on a case record form.

Other measures

To gain insight into the capability, opportunity and motivation of participants to engage in behaviour change the following questionnaires and test will be administered at T0.

- Health literacy will be measured using the Dutch version of the Set of Brief Screening Questions (SBSQ). (39, 40)
- Barriers and motivators regarding physical activity will be measured using the Barriers and Motivators Questionnaire (BMQ). (41)
- Barriers and motivators regarding nutritional intake will be measured using a subset of the Motivators and Barriers to Health-Smart Behaviours Inventory regarding health food and healthy drinks. (42)
- Barriers and motivators regarding social support will be measured using the short version of the SSL-Interaction (SSL-I). (43)
- The Self-Efficacy to Manage Chronic Disease Scale (SE-MCDS) will be used to gain insight into the confidence of a person in the ability to successfully perform a specific task or behaviour related to one's health in various situations. (44, 45)
- Personal control will be measured using the Pearlin-Schooler Mastery Scale. (38, 45)
- To gain insight into goal directedness and action planning skills of participants, the Action and Coping planning questionnaire developed by Sniehotta et al. will be used. (46)

- The Montreal Cognitive Assessment (MoCA) will be used a screening tool for cognitive deterioration. (47)

Mixed-method study implementation

Data regarding feasibility and acceptability of the prehabilitation program will be collected throughout the study period. To assess feasibility the following data will be collected:

- Enrolment (number of eligible participants, consent rate, reasons for refusal (if known))
- Attrition (percentage of completion of the program, reasons for drop-out)
- Fidelity (adherence to the program, barriers and facilitators; adjustments to the program)
- Safety (number of adverse events)
- Logistical problems

The acceptability of the prehabilitation program will be assessed among participants using the Treatment Acceptability and Preference (TAP) questionnaire and among involved healthcare professionals using the NoMAD questionnaire. (48, 49, 50) In addition, satisfaction, feedback regarding the program, barriers and facilitators for further implementation will be obtained by focus group meetings with participants of the intervention group and involved healthcare providers at the end of the study period.

Demographic and patient characteristics will be recorded throughout the study.

Sample size calculation

An a priori sample-size calculation was performed based on an effect size of 0.5, which is generally found across outcomes and across populations as indicative of a minimal clinically important difference. To find a statistically significant difference between the control and intervention groups in the change of frailty at the end of the prehabilitation program (T1) with a medium effect size (0.5), alpha-value of 0.05 (2-sided) and a power of 0.80 at least 128

participants are needed in the study, n = 64 in each group. Based on a drop-out rate of 15%, 148 KTCs will be needed for randomization. Given the estimated exclusion after the assessment of participants with no problems of 15%, 176 KTCs need to be included for assessment.

Based on a conservative estimation of 50% regarding response rate to the invitation to participate in the study, and an initial exclusion of 10% of the target population (e.g., because of a language barrier), a total of 388 KTCs (2x 176 needed for assessment + 10% exclusion) will be needed as potential eligible participants.

Statistical analysis

All analyses will be performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 28.0. IBM Corp., Armonk, NY, USA). The analyses will be based on the intention-to-treat principal. A two-sided p-value of <0.05 will be considered to indicate statistical significance for all analyses.

An intention to treat analysis will be carried out to study the difference in outcome measures between the intervention and the control group. The primary outcome will be the change in frailty status between T0 and T1. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data.

Explorative analysis will be performed to gain insight into differences between the intervention and the control group regarding changes in frailty status (T1-T2), physical functioning, nutritional status, psychosocial well-being, quality of life and clinical outcomes at the various

measurement points. These changes will be analysed using the appropriate tests based on measurement level and distribution. Differences in proportions between groups will be examined using Chi-square tests. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data. Changes over time between T0- T2 will be analysed using General Linear Models analysis with group*time interaction.

Data regarding feasibility, acceptability and barriers and facilitators for further implementation (e.g., enrolment, attrition, adherence, safety, logistical problems) will be described using descriptive statistics.

Qualitative data from the focus group meetings will be audio recorded and transcribed verbatim. Transcriptions will be imported into Atlas.ti 22 (Scientific Software development GmbH, Berlin, Germany). Data will be iteratively analysed and discussed using six analysis steps: familiarization with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and writing the report. (51, 52)

Data management

Data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (UAVG). All participant data will be pseudonymized. A key list (identification list) will be kept to be able to link data of the electronic patient dossier to a pseudonymized patient. This key list will be secured by a password and saved on a locked research drive. Hardcopy research data of the project will be stored in a locked filing cabinet in the office of the principal investigator,

which will also be locked. After the completion of the research project, as soon as all research data have been analysed and processed, all hardcopy research documents will be sent to the central archive of the UMCG.

ETHICS AND DISSEMINATION

Medical ethical approval for this study has been granted Institutional Review Board of the UMCG (registration no. METc 2022/421). The study will adhere to institutional policies, local laws and the Declaration of Helsinki.

Although the risk of injury during exercise is negligible, this will be monitored weekly by a lifestyle coach. All adverse events will be followed until they have abated, or until a stable situation has been reached.

The results will be disseminated at international conferences and in peer-reviewed journals.

Authors' contributions

The protocol was designed and written by CA and EEQ. It was critically reviewed by AH, YV, HM, SB, AR, SJLB, EF and RAP. All authors approved the final version of this manuscript.

Funding

This work was supported by The Dutch Kidney Foundation, grant number 20OS008.

Competing interests statement

The authors declare no conflicts of interest.

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TABLES

Table 1: Overview of questionnaires and measurements at various measurement points

	Baseline (T0)	Week 13 (T1)	Week 26 (T2)
Measurements at home			
• Food diary (3 days)	x	x	x
• Activity tracker (3 days)	x	x	x
Questionnaires (online or paper-and pencil)			
Physical activity			
• Duke Activity Status Index (DASI)	X	X	X
Nutritional Status			
• Patient-Generated Subjective Global assessment (PG-SGA- SF)	X	X	X
Psychological fitness			
• State-Trait Anxiety Inventory (STAI-6)	X	X	X
• Patient Health Questionnaire (PHQ-9)	X	X	X
• Checklist Individual Strength (CIS-8)	X	X	X
Outcomes			
• HRQoL- SF36	X	X	X
Questionnaires Com-B model			
Capability			
• *Capability*	X		
• Health Literacy (SBSQ-D)			
• *Physical ability*			
• Physical subscale SF36	(X)		
• Duke Activity Status Index (DASI)	(X)		
Opportunity			
• *Social influences*			
• Social support (SSL-I)	X		
• *Environmental context and resources*			
• Barriers and motivators questionnaire	X		
• Health-Smart behaviour inventory	X		
Motivation			
• *Beliefs about capabilities*			
• Self-efficacy (SE-MCDS)	X		
• Personal control (Mastery Scale)	X		
• *Goals & Planning*			
• Action planning and control planning questionnaire	X		
Tests and questionnaires during study visit			
Physical activity			
• Handgrip strength	X	X	X
• Biceps strength	X	X	X
• Quadriceps strength	X	X	X
• Short Physical Performance Battery	X	X	X
• Steep ramp test	X	X	X
• Short Questionnaire to assess health-enhancing physical activity (SQUASH)	X	X	X
Nutritional status			
• Bio-impedance analysis (BIA)	X	X	X
• BMI (Height & Weight measurement)	X	X	X
• Hip-waist ratio	X	X	X
Cognitive ability			
• Montreal Cognitive Assessment	X		
Outcomes			
• Tilburg Frailty Indicator	x	x	x

FIGURE LEGENDS

Figure 1: Overview PreCareTx study

Figure 2: Components of the physical activity intervention and examples of possible activities

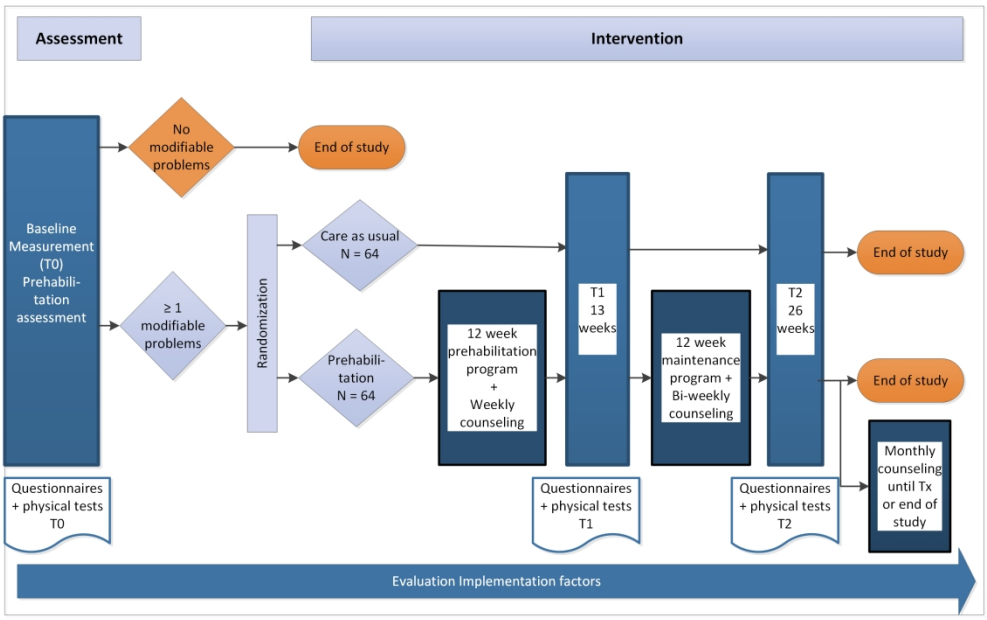

Figure 1: Overview PreCareTx study

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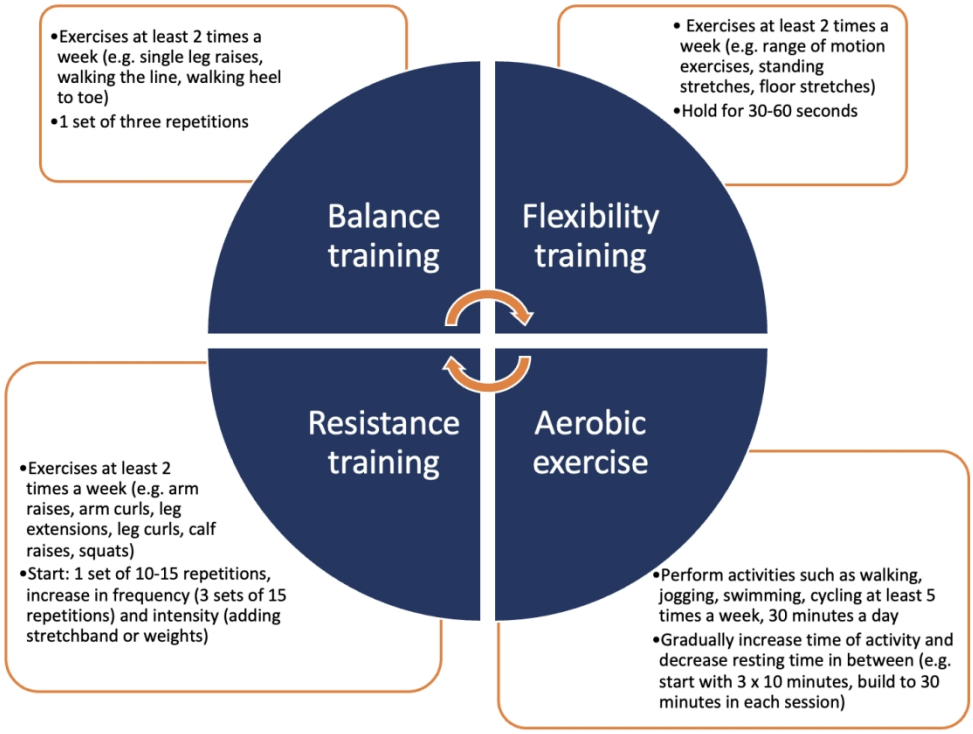

Figure 2: Components of the physical activity intervention and examples of possible activities

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BMJ Open

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study: protocol for a hybrid type I, mixed method, randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-072805.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Jun-2023
Complete List of Authors:	Quint, Evelien; University Medical Centre Groningen, Surgery Haanstra, Avril J.; University of Groningen, Department of Health Sciences van der Veen, Yvonne; University of Groningen, Department of Health Sciences; University of Groningen, Department of Internal Medicine Maring, Heleen; University of Groningen, Department of Health Sciences; University Medical Center Groningen, Department of Physical Therapy Berger, Stefan; Universitair Medisch Centrum Groningen, Nephrology Ranchor, Adelita; University of Groningen Bakker, Stephan; University of Groningen, University Medical Center Groningen, Internal Medicine Finnema, Evelyn; University Medical Centre Groningen, Department of Health Science Pol, Robert; University Medical Centre Groningen, Surgery Annema, Coby; University of Groningen, Department of Health Sciences
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine, Surgery
Keywords:	Renal transplantation < NEPHROLOGY, NUTRITION & DIETETICS, Rehabilitation medicine < INTERNAL MEDICINE, MENTAL HEALTH, Quality of Life

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study: protocol for a hybrid type I, mixed method, randomized controlled trial

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ABSTRACT

Introduction: Kidney transplant candidates (KTCs) need to be in optimal physical and psychological condition prior to surgery. However, KTCs often experience compromised functional capacity which can be characterized as frailty. Prehabilitation, the enhancement of a person's functional capacity, may be an effective intervention to improve the health status of KTCs. The PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study aims to examine the effectiveness of a multi-modal prehabilitation program on the health status of KTCs, and to explore the potential of implementation of prehabilitation in daily clinical practice.

Methods and analysis: This study utilizes a single centre, effectiveness-implementation hybrid type I study design, comprised of a randomized controlled trial and a mixed-methods study. Adult patients who are currently on the transplant waiting list or are waitlisted during the study period, at a university medical centre in The Netherlands, will be randomly assigned to either prehabilitation (n=64) or care as usual (n=64) groups. The prehabilitation group will undergo a 12-week home-based, tailored prehabilitation program consisting of physical and/or nutritional and/or psychosocial interventions depending on the participant's deficits. This program will be followed by a twelve-week maintenance program in order to enhance the incorporation of the interventions into daily life. The primary endpoint of this study is a change in frailty status as a proxy for health status. Secondary endpoints include changes in physical fitness, nutritional status, psychological well-being, quality of life and clinical outcomes. Tertiary endpoints include the safety, feasibility and acceptability of the prehabilitation program, and the barriers and facilitators for further implementation.

Ethics and dissemination: Medical ethical approval was granted by the Medical Ethics Committee Groningen, The Netherlands (M22.421). Written informed consent will be obtained from all participants. The results will be disseminated at international conferences and in peer-reviewed journals. Trial registration number: NCT05489432, ClinicalTrials.gov.

Strengths and limitations of this study

- The intervention was developed in co-creation with kidney transplant candidates and recipients, their significant others and healthcare providers involved in kidney transplant care.
- A randomized controlled trial will provide a high-quality assessment of the effect of a multimodal, tailor-made prehabilitation program on frailty and other important patient-centred outcomes regarding physical fitness, nutritional status and psychosocial well-being.
- A mixed methods study will provide insight into the feasibility and acceptability of prehabilitation in a real-world setting by analysing the barriers and facilitators associated with this intervention.
- This single-centre study only includes kidney transplant candidates.
- The study is not double-blinded due to the nature of the intervention.

INTRODUCTION

Kidney transplant candidates (KTCs) may have a compromised health status due to disease progression, comorbidities, and the adverse effects of dialysis. This may lead to impaired physical fitness, lower quality of life, and an increased risk of developing psychological problems. (1, 2, 3, 4, 5) Poor health status is related to a low level of physical activity, eliciting a cycle of deteriorating physical fitness in which multiple factors are involved, including muscle wasting, malnutrition, inflammation, and fatigue. (4) Data from the TransplantLines Biobank & Cohort study (6) at our centre, the University Medical Center Groningen (UMCG), showed that of 424 KTCs, 87% had one or more problems related to physical or psychological fitness prior to transplantation. Regarding physical fitness, 55% of KTCs had problems related to decreased muscle strength and/or walking ability and 45% had a suboptimal nutritional status. Concerning psychological well-being, 36% showed high symptom levels of anxiety and/or depression. In addition, 58% of the KTCs experienced severe fatigue and 19% experienced moderate fatigue. These findings show that KTCs are a vulnerable patient population and exhibit signs of frailty. Frailty is a multidimensional syndrome and captures the multiple domains involved in the health status of KTCs. It is a physiological condition caused by declines across physical, cognitive and physiological reserves. (7, 8, 9) Among KTCs, frailty is associated with an increased inflammatory state, hospitalizations and waitlist mortality. (10, 11, 12) It is estimated that one in six kidney transplant recipients is frail prior to transplantation. (13)

Studies have shown that physical fitness and psychological wellbeing can be improved by the means of prehabilitation. (14, 15, 16, 17, 18) Prehabilitation is an intervention aimed at optimizing the patient's overall fitness before an operation to enhance recovery after the surgery and improve outcomes. Prehabilitation may also be effective in improving the overall health status of KTCs prior to the kidney transplant. It focuses on implementing lifestyle changes in

order to enable patients to withstand the stress of surgery, reduce the risk of post-operative complications, unplanned readmissions, and to enhance recovery. (19) Prehabilitation comprises physical training, dietary management, and psychosocial interventions. (19) The waiting list period before the kidney transplant provides a window of opportunity to improve the overall fitness of KTCs by prehabilitation. In the Netherlands, the duration of the waiting-list period ranges from less than 3 months for those who receive a kidney from a living donor to over three years in case of deceased donor kidney transplantation. Especially for the latter, the duration of the waiting-list period is unpredictable. By offering a prehabilitation program tailored to the needs and possibilities of KTCs prior to transplantation, patients may be more likely to adopt a sustainable, healthy lifestyle.

Studies have shown that prehabilitation during the waiting-list period in transplant candidates is feasible. (15, 18, 20, 21, 22) Three studies showed that prehabilitation significantly improved physical activity, fatigue, walking time, and grip strength during the waitlist period in KTCs. (18, 20, 21) However, these studies had a small sample size, and the interventions were not provided in a multimodal approach. As KTCs experience deficits across multiple reserves, a multimodal approach is essential. Additionally, complex interactions between the physical and psychological health of a patient are addressed when multimodal interventions are implemented. (23) Therefore, the effectiveness of a multimodal tailored prehabilitation program in KTCs still needs to be determined.

The primary objective of this study is to measure the effect of a 12-week home-based, tailor-made multimodal prehabilitation program on changes in frailty status between T0 (screening for modifiable problems) and T1 (13 weeks after start of the prehabilitation program). Furthermore, changes in physical functioning, nutritional status, psychological wellbeing, quality of life and clinical outcomes between T0 and T1 will be measured.

The secondary objectives are to determine the sustainability of the results regarding frailty status and changes in physical functioning, nutritional status, psychological wellbeing and quality of life at 6 months after the start of the study.

The tertiary objective of this study is to explore the potential for further implementation of prehabilitation in a daily clinical practice. This will be done by examining the safety, feasibility and acceptability of the prehabilitation program and barriers and facilitators for further implementation.

METHODS AND ANALYSIS

Trial design

The PreCareTx study utilizes a single centre, effectiveness-implementation hybrid type 1 study design, consisting of a randomized controlled trial and a mixed methods study. An overview of the study is given in Figure 1. The duration of the study will be three years, starting in January 2023. The study is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement. (24) The study has been registered on ClinicalTrials.gov (NCT05489432).

Study setting

The intervention will be conducted in the KTCs' home environment, depending on their needs and preferences. Study visits will be conducted at the UMCG in The Netherlands at the following time points: baseline (T0), and at week 13 (T1) and week 26 (T2) after randomization.

Recruitment

Patients on the UMCG waiting list for kidney transplantation or waitlisted during the inclusion period, will be recruited by their treating physician and receive an information letter about the

risks and benefits of the study. Written informed consent will be obtained from the patient. Patient recruitment will start in January 2023 and end in June 2025.

Eligibility criteria

In order to be eligible to participate in this study, potential participants must meet all the following inclusion criteria:

1) Adult kidney transplant candidate (≥18 years).
2) Listed for kidney transplantation on the UMCG kidney transplant waiting list at the start of the study or waitlisted during the inclusion period (January 2023 – June 2025).

The exclusion criteria include:

1) Inability to read and/or speak the Dutch language.
2) Combined organ transplantation (e.g., kidney+pancreas, kidney+liver).
3) In case of living donor kidney transplant: a transplantation planned within 3 months.
4) Involved in a lifestyle intervention study.

Participant screening & assessment

After informed consent, participants will be screened for problems regarding physical activity, nutritional status or psychological wellbeing in an assessment.

To evaluate physical functioning, participants will complete several questionnaires, including the Duke Activity Status Index (DASI), the physical subscale of the Short Form 36 (SF-36) and the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH). Additionally, participants will wear an activity tracker for three days and their handgrip-,

bicep- and quadricep strength will be measured. Furthermore, the Short Physical Performance Battery (SPPB) and the steep ramp test (SRT) will be performed.

To assess nutritional status, participants will complete the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) and maintain a food diary for three days. In addition, the participant's hip-waist ratio and their Body Mass Index (BMI) will be measured. Lastly, a Bio-impedance analysis (BIA) will be conducted.

For the evaluation of psychological functioning, participants will be asked to complete the following questionnaires: State-Trait Anxiety Inventory (STAI6), Patient Health Questionnaire 9 (PHQ-9) and Checklist Individual Strength: subjective fatigue (CIS8R). Finally, the Montreal Cognitive Assessment will be administered.

To assess frailty status and health-related quality of life (HRQoL), each participant will complete the Tilbury Frailty Indicator (TFI) and the SF-36, respectively.

The details of the assessment are described in Table 1 and under *Outcome measurements*. Participants who present with one or more modifiable problem(s) will be eligible to take part in the intervention study. In this study, a modifiable problem is defined as a problem that can be altered by the means of prehabilitation.

Randomization and allocation concealment

All participants who present with at least one modifiable problem, as determined during the assessment at the baseline study visit, will be randomized to the intervention or control group on a 1:1 ratio using block randomization after stratification for sex and pre-emptive/non-pre-

emptive transplantation. This study will not be blinded as it is not possible to blind the participant, or healthcare professionals involved in the intervention. Randomization will take place using ALEA (www.aleaclinical.eu). The randomization will be performed by an independent researcher who is not involved in screening, recruitment, clinical care, or data collection.

Intervention

The home-based, multi-modal, tailor-made program will focus on three domains (physical activity, nutritional advice, and psychosocial support) depending on the preferences and needs of the participant. For each domain, interventions have been developed based on the behavioural change wheel (BCW) method. (16, 17) A context analysis was performed to gain insight into the problems KTCs face, and the factors (i.e., preferences, barriers, limitations and facilitating factors) that are important to them for the creation and implementation of a prehabilitation program. Two certified lifestyle coaches, a physiotherapist and a dietitian, will be involved in the intervention. The lifestyle coach, together with the participant and their significant other, will compose a personalized, goal-directed prehabilitation program that can be incorporated into the daily life of the participant. During the intervention, the lifestyle coach will provide (bi)weekly counselling sessions with the participant. In these sessions, the progress of the participant, including their goals, facilitators and barriers, will be discussed. Participants will be offered monthly counselling sessions after completing the maintenance program. Counselling ends when the participant chooses not to make use of the counselling sessions and/or when they undergo KT.

Physical activity

The aim of the physical activity interventions will be to improve the strength and endurance of KTCs. The criteria of The Nederlandse Norm Gezond Bewegen (NNGB, in English: Dutch Healthy Physical Activity Guidelines), which includes: 1) performing activities that are moderately intense in nature for at least 30 minutes a day/five days per week, and 2) performing activities to increase muscle strength for 20 minutes a day/ 2-3 days a week, will serve as guidance. (25) The intervention will differ per participant depending on his/her baseline fitness level, preferences and whether or not they are on dialysis. (26) Figure 2 shows the various components which will be considered whilst creating the tailor-made intervention for each participant.

Nutritional advice

Nutritional interventions will focus on improving nutritional status and body composition by supporting participants to engage in healthy and sustainable dietary habits. If participants already receive guidance from a dietician in the context of regular care, the nutritional advice will be coordinated with his/her dietician. The intervention will be tailored to the nutritional problems and/or dietary restrictions of each individual participant and focus on optimizing and preventing shortages or imbalances of energy, protein and/or other nutrients for all participants.

Psychosocial support

Psychosocial interventions will consist of individual coaching by a certified lifestyle coach during (bi)weekly counselling sessions. The sessions will focus on the use of effective coping strategies, stress and energy management, and promoting social support. Significant others may take part in these sessions if the participant wishes that they do. In addition, interventions aimed at relaxation such as sleep hygiene and

relaxation interventions (e.g., progressive muscle relaxation techniques, visual and auditory stimulation, breathing techniques) will be offered. Participants with clinically relevant scores regarding anxiety (STAI6 ≥12) or depression (PHQ-9 ≥10) will be referred to a social worker at their local hospital for further evaluation, treatment and/or referral to a psychologist. (27, 28)

Control group

The control group will receive care as usual. Standard medical care for KTCs consists of a consult with a nephrologist and/or nurse practitioner at their local hospital every three months approximately. In addition, a consult with a dietician is scheduled if laboratory values are not consistent with expected results from dietary restrictions for chronic kidney disease or upon demand of the KTC. Depending on the needs of the KTC a social worker can be consulted. Regarding measurements, the same time intervals will be used in between assessments. A study visit at the UMCG will be planned at week 13 (T1) and week 26 (T2) after randomization.

Withdrawal participant

Participants may always withdraw from the study, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants will be withdrawn if they get transplanted during the study.

If participants withdraw from the study prior to measurement point T1, new participants will be included to ensure sufficient power of the study. Participants who have withdrawn from the study after T1 but indicate that their data may be used in the follow-up studies (e.g., on the

effect of prehabilitation on outcomes after transplantation) will be followed according to the specifications of the patient.

Outcome measurements

All outcome measurements are summarized in Table 1. The primary, secondary and clinical outcomes will be measured at three timepoints: T0 (baseline assessment), T1 (week 13) and T2 (week 26). If a participant is unable to make it to the study visit at week 13 or week 26, a study visit will be planned within a one-week time frame of these timepoints.

Primary outcome

The primary outcome will be change in frailty status between T0 and T1 as measured by the TFI. (29) This validated tool has been chosen as it covers multiple components of frailty. In addition, the sustainability of the intervention will be examined by change in frailty status between T1 and T2. The TFI is a multidimensional, validated questionnaire for measuring frailty among community dwelling older adults. (29) It consists of 15 items reflecting the different components of frailty: physical frailty (8 items), psychological frailty (4 items) and social frailty (3 items). The total TFI score ranges between 0-15. A score ≥5 is used as a cut-off point for frailty.

Secondary outcomes

Secondary endpoints include changes in physical functioning, nutritional status, psychological well-being and quality of life. To measure these changes, a set of questionnaires will be filled out prior to the study visits (T0/T1/T2) in the UMCG using an online survey. Participants who prefer a pen-and-paper survey, will receive one via mail. Physical tests will be done during the study visit at the UMCG.

Physical functioning will be measured by two questionnaires and five performance tests.

- The SQUASH will be used to gain insight into engagement in physical activities in one's daily life. (30)
- The DASI will be used to measure functional capacity. (31)
- An activity tracker will be used to measure the number of steps taken by the participant. Participants will be asked to wear the activity tracker for three days and note the steps per day in their food diary (see nutritional assessment).
- Handgrip strength will be assessed using the Jamar Hydraulic Hand Dynamometer (Patterson Medical JAMAR 5030J1, Warrenville, Canada). (32)
- Quadricep and bicep strength will be measured with a hand-held dynamometer CITEC CT 3002/30 handheld dynamometer (Haren, The Netherlands). (33, 34)
- The SPPB will be used to measure physical performance regarding balance, gait speed and leg muscle strength. (35) The SPPB consists of a balance test, a 4-meter walking test and the 5 Times Sit-To-Stand test (5TSTS).
- The SRT will be performed on an electronically braked cycle ergometer to measure one's aerobic capacity. During the SRT, the resistive load is accelerated in a fast schedule (25 W/10 sec) until exhaustion of the participant. (36)

Nutritional status will be assessed by a questionnaire, a food diary, and three body measurements.

- The PG-SGA SF will be used to assess nutritional status across various domains: changes in body weight, changes in nutritional intake, symptoms which negatively influence intake, absorption and utilization of nutrients, and level of activities and function. (37)

- Participants will be asked to complete a food diary throughout consecutive three days, including one weekend day, to gather information on fat, protein, and energy intake.
- BMI will be calculated as follows: weight (in kg) divided by height (m) squared (kg/m^2).
- Hip and waist circumference will be measured in centimetres to calculate a waist-hip ratio.
- BIA will be conducted to non-invasively measure body composition (e.g., lean tissue index, fat tissue index, extra cellular and intra cellular volume) by using the InBodyS10.

Psychosocial well-being will be measured by three questionnaires.

- Symptoms of anxiety will be measured using the short-form of the STAI-6. (38)
- Symptoms of depression will be measured using the PHQ-9. (39)
- Fatigue will be measured using the CIS8R. (39)

Health-Related Quality of Life

To assess HRQoL, the SF-36 health survey will be used. It is a 36-item, self-reported questionnaire that captures participants' perceptions of their own health and wellbeing. Based on the item scores, a physical component score (PCS) and a mental component score (MCS) will be calculated. (40, 41)

Clinical outcomes

Clinical outcomes, including waitlist mortality, delisting, and the number of hospital admissions, will be assessed by medical record review until time of transplantation and recorded on a case record form.

Other measures

To gain insight into the capability, opportunity and motivation of participants to engage in behaviour change the following questionnaires and test will be administered at T0.

- Health literacy will be measured using the Dutch version of the Set of Brief Screening Questions (SBSQ). (42, 43)
- Barriers and motivators regarding physical activity will be measured using the Barriers and Motivators Questionnaire (BMQ). (44)
- Barriers and motivators regarding nutritional intake will be measured using a subset of the Motivators and Barriers to Health-Smart Behaviours Inventory regarding health food and healthy drinks. (45)
- Barriers and motivators regarding social support will be measured using the short version of the SSL-Interaction (SSL-I). (46)
- The Self-Efficacy to Manage Chronic Disease Scale (SE-MCDS) will be used to gain insight into the confidence of a person in the ability to successfully perform a specific task or behaviour related to one's health in various situations. (47, 48)
- Personal control will be measured using the Pearlin-Schooler Mastery Scale. (41, 48)
- To gain insight into goal directedness and action planning skills of participants, the Action and Coping planning questionnaire developed by Sniehotta et al. will be used. (49)
- MoCA will be used a screening tool for cognitive deterioration. (50)

Tertiary outcomes

Data regarding feasibility and acceptability of the prehabilitation program will be collected throughout the study period. To assess feasibility the following data will be collected:

- Enrolment (number of eligible participants, consent rate, reasons for refusal (if known))

- Attrition (percentage of completion of the program, reasons for drop-out)
- Fidelity (adherence to the program, barriers and facilitators; adjustments to the program)
- Safety (number of adverse events)
- Logistical problems

The acceptability of the prehabilitation program will be assessed among participants using the Treatment Acceptability and Preference (TAP) questionnaire and among involved healthcare professionals using the NoMAD questionnaire. (51, 52, 53) In addition, satisfaction, feedback regarding the program, barriers and facilitators for further implementation will be obtained by six focus group meetings with participants of the intervention group and involved healthcare providers at the end of the study period. The focus group meetings will be led by an experienced senior researcher.

Demographic and patient characteristics will be recorded throughout the study.

Sample size calculation

An a priori sample-size calculation was performed based on an effect size of 0.5, which is generally found across outcomes and across populations as indicative of a minimal clinically important difference. To find a statistically significant difference between the control and intervention groups in the change of frailty at the end of the prehabilitation program (T1) with a medium effect size (0.5), alpha-value of 0.05 (2-sided) and a power of 0.80 at least 128 participants are needed in the study, n = 64 in each group. Based on a drop-out rate of 15%, 148 KTCs will be needed for randomization. Given the estimated exclusion after the assessment of participants with no problems of 15%, 176 KTCs need to be included for assessment.

Based on a conservative estimation of 50% regarding response rate to the invitation to participate in the study, and an initial exclusion of 10% of the target population (e.g., because

of a language barrier), a total of 388 KTCs (2x 176 needed for assessment + 10% exclusion) will be needed as potential eligible participants.

Statistical analysis

All analyses will be performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 28.0. IBM Corp., Armonk, NY, USA). The analyses will be based on the intention-to-treat principal. A two-sided p-value of <0.05 will be considered to indicate statistical significance for all analyses.

An intention to treat analysis will be carried out to study the difference in outcome measures between the intervention and the control group. The primary outcome will be the change in frailty status between T0 and T1. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data.

Regarding missing data, imputation by mean or modus will be done if missing at random (MAR) is less than 5%. If MAR >5%, multiple imputation will be utilized. Imputation will not be performed if missing data are not random.

Explorative analysis will be performed to gain insight into differences between the intervention and the control group regarding changes in frailty status (T1-T2), physical functioning, nutritional status, psychosocial well-being, quality of life and clinical outcomes at the various measurement points. These changes will be analysed using the appropriate tests based on measurement level and distribution. Differences in proportions between groups will be

examined using Chi-square tests. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data. Changes over time between T0- T2 will be analysed using General Linear Models analysis with group*time interaction.

Data regarding feasibility, acceptability and barriers and facilitators for further implementation (e.g., enrolment, attrition, adherence, safety, logistical problems) will be described using descriptive statistics.

Qualitative data from the focus group meetings will be audio recorded and transcribed verbatim. Transcriptions will be imported into Atlas.ti 22 (Scientific Software development GmbH, Berlin, Germany). Data will be iteratively analysed and discussed using six analysis steps: familiarization with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and writing the report. (54, 55)

Data management

Data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (UAVG). All participant data will be pseudonymized. Data collection forms will be stored in RoQua and REDCap. A key list (identification list) will be kept to be able to link data of the electronic patient dossier to a pseudonymized patient. This key list will be secured by a password and saved on a locked research drive. Hardcopy research data of the project will be stored in a locked filing cabinet in the office of the principal investigator, which will also be locked. The principal investigator will have access to the final trial dataset. After the completion of the

research project, as soon as all research data have been analysed and processed, all hardcopy research documents will be sent to the central archive of the UMCG.

Data monitoring

The principal investigator has deemed the implementation of a data monitoring committee unnecessary due to the low-risk nature of this study.

PATIENT AND PUBLIC INVOLVEMENT

The patient advisory committee (PAC) of the UMCG Transplant Center was involved in the process of development of the study by exchanging ideas and giving feedback on the research proposal. The patient council of the Dutch Kidney Foundation contributed to the acceptance of the grant that helped fund this study. Also, a context analysis was performed to gain insight into the problems that KTCs face and the help that they receive prior to transplantation.

The project's steering committee consists of patients, including a representative of the PAC of the Transplant Center, and professionals. This group discusses the progress of the study quarterly.

Patients will be involved in further development of the prehabilitation program.

ETHICS AND DISSEMINATION

Medical ethical approval for this study has been granted Institutional Review Board of the UMCG (registration no. METc 2022/421). The study will adhere to institutional policies, local laws and the Declaration of Helsinki. Written informed consent will be obtained from all

participants by their treating physician. Important protocol modifications will be communicated to relevant parties.

Although the risk of injury during exercise is negligible, this will be monitored weekly by a lifestyle coach. All adverse events will be followed until they have abated, or until a stable situation has been reached.

The results will be disseminated at international conferences and in peer-reviewed journals.

Authors' contributions

The protocol was designed and written by CA and EEQ. It was critically reviewed by AH, YV, HM, SB, AR, SJLB, EF and RAP. All authors approved the final version of this manuscript.

Roles and responsibilities

Principal investigator: design and conduct of PreCareTx; preparation of protocol and revisions; preparation of investigators brochures and case report forms; organising steering committee meetings; publication of study reports.

PhD student: recruitment of patients; coordinating and supervising research students and lifestyle coaches; performing data analysis.

Steering committee: reviewing progress of the study; agreement of final protocol.

Funding

This work was supported by The Dutch Kidney Foundation, grant number 20OS008. This funding source had no role in the design of this study, nor will it have any role during its execution.

Trial sponsor

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Competing interests statement

The authors declare no conflicts of interest.

Protocol version

Issue date: 13 February 2023, version 1.0

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TABLES

Table 1: Overview of questionnaires and measurements at various measurement points

	Baseline (T0)	Week 13 (T1)	Week 26 (T2)
Measurements at home			
• Food diary (3 days)	x	x	x
• Activity tracker (3 days)	x	x	x
Questionnaires (online or paper-and pencil)			
Physical activity			
• Duke Activity Status Index (DASI)	X	X	X
Nutritional Status			
• Patient-Generated Subjective Global assessment (PG-SGA- SF)	X	X	X
Psychological fitness			
• State-Trait Anxiety Inventory (STAI-6)	X	X	X
• Patient Health Questionnaire (PHQ-9)	X	X	X
• Checklist Individual Strength (CIS-8)	X	X	X
Outcomes			
• HRQoL- SF36	X	X	X
Questionnaires Com-B model			
Capability			
• *Capability*	X		
• Health Literacy (SBSQ-D)			
• *Physical ability*			
• Physical subscale SF36	(X)		
• Duke Activity Status Index (DASI)	(X)		
Opportunity			
• *Social influences*			
• Social support (SSL-I)	X		
• *Environmental context and resources*			
• Barriers and motivators questionnaire	X		
• Health-Smart behaviour inventory	X		
Motivation			
• *Beliefs about capabilities*			
• Self-efficacy (SE-MCDS)	X		
• Personal control (Mastery Scale)	X		
• *Goals & Planning*			
• Action planning and control planning questionnaire	X		
Tests and questionnaires during study visit			
Physical activity			
• Handgrip strength	X	X	X
• Biceps strength	X	X	X
• Quadriceps strength	X	X	X

• Short Physical Performance Battery	X	X	X
• Steep ramp test	X	X	X
• Short Questionnaire to assess health-enhancing physical activity (SQUASH)	X	X	X
Nutritional status			
• Bio-impedance analysis (BIA)	X	X	X
• BMI (Height & Weight measurement)	X	X	X
• Hip-waist ratio	X	X	X
Cognitive ability			
• Montreal Cognitive Assessment	X		
Outcomes			
• Tilburg Frailty Indicator	x	x	x

FIGURE LEGENDS

Figure 1: Overview PreCareTx study

Figure 2: Components of the physical activity intervention and examples of possible activities

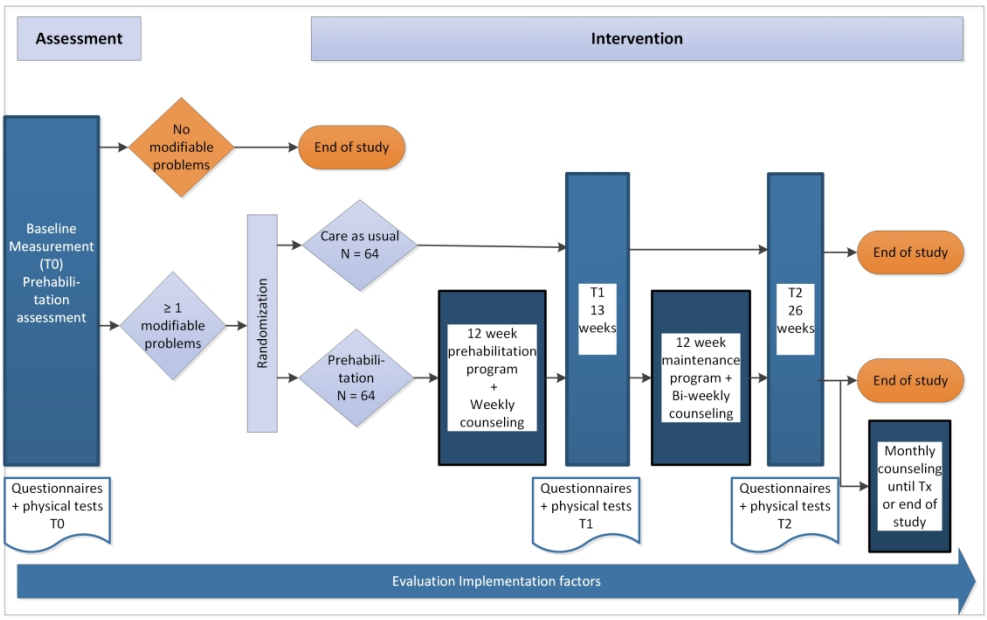

Figure 1: Overview PreCareTx study

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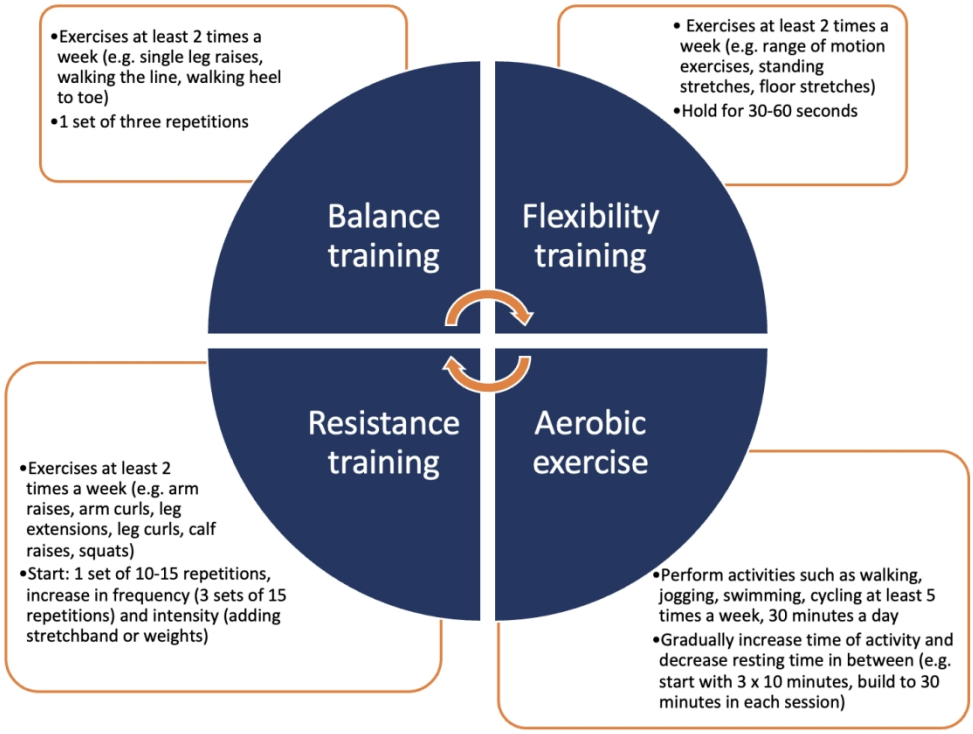

Figure 2: Components of the physical activity intervention and examples of possible activities

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1, line 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (page 3, line 5)
	2b	All items from the World Health Organization Trial Registration Data Set (N/A)
Protocol version	3	Date and version identifier (page 23, line 1-2)
Funding	4	Sources and types of financial, material, and other support (page 22, line 14-17)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (page 1, lines 4-17; page 22, line 1-4)
	5b	Name and contact information for the trial sponsor (page 22, lines 19-21)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (page 22, lines 14-17)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (page 22, lines 6-12).
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (page 5, line 21-25; page 6, line 1-19)
	6b	Explanation for choice of comparators (page 6, line 18-19)

Objectives	7	Specific objectives or hypotheses (page 6, line 20-24; page 7, line 1-7)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (page 7, line 9-11)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 7, line 17-19)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (page 8, line 4-19)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (page 10, line 11-25; page 11-12)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (page 12, line 22-24)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (page 10, line 21-25)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (page 8, line 19)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (page 13, line 7-25; page 14-17)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (page 17, line 17-23; page 1-7)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 7, line 22-24)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 10, line 6-7)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (page 10, line 5-6)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 10, line 7-9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (N/A; page 10, line 5-6)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (N/A)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (page 13-17; page 19, line 25)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (page 13, line 1-5)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (page 20, line 1-7)

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (page 18, line 15-20)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (page 19, line 1-20)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (page 18, line 22-24)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (page 20, line 9-11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (N/A)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (page 21, line 8-10)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (N/A)
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (page 21, line 1-3)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (page 21, line 5-6)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 21, line 4-5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N/A)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (page 20, line 1-7)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 22, line 3-4)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (page 20, line 4-5)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (N/A)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (page 21, line 12)
	31b	Authorship eligibility guidelines and any intended use of professional writers (N/A)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (N/A)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (Available upon request)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (N/A)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study: protocol for a hybrid type I, mixed method, randomized controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-072805.R2
Article Type:	Protocol
Date Submitted by the Author:	13-Jul-2023
Complete List of Authors:	Quint, Evelien; University Medical Centre Groningen, Surgery Haanstra, Avril J.; University of Groningen, Department of Health Sciences van der Veen, Yvonne; University of Groningen, Department of Health Sciences; University of Groningen, Department of Internal Medicine Maring, Heleen; University of Groningen, Department of Health Sciences; University Medical Center Groningen, Department of Physical Therapy Berger, Stefan; Universitair Medisch Centrum Groningen, Nephrology Ranchor, Adelita; University of Groningen Bakker, Stephan; University of Groningen, University Medical Center Groningen, Internal Medicine Finnema, Evelyn; University Medical Centre Groningen, Department of Health Science Pol, Robert; University Medical Centre Groningen, Surgery Annema, Coby; University of Groningen, Department of Health Sciences
Primary Subject Heading:	Renal medicine
Secondary Subject Heading:	Rehabilitation medicine, Surgery
Keywords:	Renal transplantation < NEPHROLOGY, NUTRITION & DIETETICS, Rehabilitation medicine < INTERNAL MEDICINE, MENTAL HEALTH, Quality of Life

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study: protocol for a hybrid type I, mixed method, randomized controlled trial

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ABSTRACT

Introduction: Kidney transplant candidates (KTCs) need to be in optimal physical and psychological condition prior to surgery. However, KTCs often experience compromised functional capacity which can be characterized as frailty. Prehabilitation, the enhancement of a person's functional capacity, may be an effective intervention to improve the health status of KTCs. The PREhabilitation of CAndidates for REnal Transplantation (PreCareTx) study aims to examine the effectiveness of a multi-modal prehabilitation program on the health status of KTCs, and to explore the potential of implementation of prehabilitation in daily clinical practice.

Methods and analysis: This study utilizes a single centre, effectiveness-implementation hybrid type I study design, comprised of a randomized controlled trial and a mixed-methods study. Adult patients who are currently on the transplant waiting list or are waitlisted during the study period, at a university medical centre in the Netherlands, will be randomly assigned to either prehabilitation (n=64) or care as usual (n=64) groups. The prehabilitation group will undergo a 12-week home-based, tailored prehabilitation program consisting of physical and/or nutritional and/or psychosocial interventions depending on the participant's deficits. This program will be followed by a twelve-week maintenance program in order to enhance the incorporation of the interventions into daily life. The primary endpoint of this study is a change in frailty status as a proxy for health status. Secondary endpoints include changes in physical fitness, nutritional status, psychological well-being, quality of life and clinical outcomes. Tertiary endpoints include the safety, feasibility and acceptability of the prehabilitation program, and the barriers and facilitators for further implementation.

Ethics and dissemination: Medical ethical approval was granted by the Medical Ethics Committee Groningen, Netherlands (M22.421). Written informed consent will be obtained

from all participants. The results will be disseminated at international conferences and in peer-reviewed journals.

Trial registration:

ClinicalTrials.gov, NCT05489432.

Strengths and limitations of this study

- The intervention was developed in co-creation with kidney transplant candidates and recipients, their significant others and healthcare providers involved in kidney transplant care.
- A randomized controlled trial will provide a high-quality assessment of the effect of a multimodal, tailor-made prehabilitation program on frailty and other important patient-centred outcomes regarding physical fitness, nutritional status and psychosocial well-being.
- A mixed methods study will provide insight into the feasibility and acceptability of prehabilitation in a real-world setting by analysing the barriers and facilitators associated with this intervention.
- This study is being conducted at a single centre and only includes kidney transplant candidates.
- The study is not double-blinded due to the nature of the intervention.

INTRODUCTION

Kidney transplant candidates (KTCs) may have a compromised health status due to disease progression, comorbidities, and the adverse effects of dialysis. This may lead to impaired physical fitness, lower quality of life, and an increased risk of developing psychological problems. (1, 2, 3, 4, 5) Poor health status is related to a low level of physical activity, eliciting a cycle of deteriorating physical fitness in which multiple factors are involved, including muscle wasting, malnutrition, inflammation, and fatigue. (4) Data from the TransplantLines Biobank & Cohort study (6) at our centre, the University Medical Center Groningen (UMCG), showed that of 424 KTCs, 87% had one or more problems related to physical or psychological fitness prior to transplantation. Regarding physical fitness, 55% of KTCs had problems related to decreased muscle strength and/or walking ability and 45% had a suboptimal nutritional status. Concerning psychological well-being, 36% showed high symptom levels of anxiety and/or depression. In addition, 58% of the KTCs experienced severe fatigue and 19% experienced moderate fatigue. These findings show that KTCs are a vulnerable patient population and exhibit signs of frailty. Frailty is a multidimensional syndrome and captures the multiple domains involved in the health status of KTCs. It is a physiological condition caused by declines across physical, cognitive and physiological reserves. (7, 8, 9) Among KTCs, frailty is associated with an increased inflammatory state, hospitalizations and waitlist mortality. (10, 11, 12) It is estimated that one in six kidney transplant recipients is frail prior to transplantation. (13)

Studies have shown that physical fitness and psychological wellbeing can be improved by the means of prehabilitation. (14, 15, 16, 17, 18) Prehabilitation is an intervention aimed at optimizing the patient's overall fitness before an operation to enhance recovery after the surgery and improve outcomes. Prehabilitation may also be effective in improving the overall health status of KTCs prior to the kidney transplant. It focuses on implementing lifestyle changes in

order to enable patients to withstand the stress of surgery, reduce the risk of post-operative complications, unplanned readmissions, and to enhance recovery. (19) Prehabilitation comprises physical training, dietary management, and psychosocial interventions. (19) The waiting list period before the kidney transplant provides a window of opportunity to improve the overall fitness of KTCs by prehabilitation. In the Netherlands, the duration of the waiting-list period ranges from less than 3 months for those who receive a kidney from a living donor to over three years in case of deceased donor kidney transplantation. Especially for the latter, the duration of the waiting-list period is unpredictable. By offering a prehabilitation program tailored to the needs and possibilities of KTCs prior to transplantation, patients may be more likely to adopt a sustainable, healthy lifestyle.

Studies have shown that prehabilitation during the waiting-list period in transplant candidates is feasible. (15, 18, 20, 21, 22) Three studies showed that prehabilitation significantly improved physical activity, fatigue, walking time, and grip strength during the waitlist period in KTCs. (18, 20, 21) However, these studies had a small sample size, and the interventions were not provided in a multimodal approach. As KTCs experience deficits across multiple reserves, a multimodal approach is essential. Additionally, complex interactions between the physical and psychological health of a patient are addressed when multimodal interventions are implemented. (23) Therefore, the effectiveness of a multimodal tailored prehabilitation program in KTCs still needs to be determined.

The primary objective of this study is to measure the effect of a 12-week home-based, tailor-made multimodal prehabilitation program on changes in frailty status between T0 (screening for modifiable problems) and T1 (13 weeks after start of the prehabilitation program). Furthermore, changes in physical functioning, nutritional status, psychological wellbeing, quality of life and clinical outcomes between T0 and T1 will be measured.

The secondary objectives are to determine the sustainability of the results regarding frailty status and changes in physical functioning, nutritional status, psychological wellbeing and quality of life at 6 months after the start of the study.

The tertiary objective of this study is to explore the potential for further implementation of prehabilitation in a daily clinical practice. This will be done by examining the safety, feasibility and acceptability of the prehabilitation program and barriers and facilitators for further implementation.

METHODS AND ANALYSIS

Trial design

The PreCareTx study utilizes a single centre, effectiveness-implementation hybrid type 1 study design, consisting of a randomized controlled trial and a mixed methods study. An overview of the study is given in Figure 1. The duration of the study will be three years, starting in January 2023. The study is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) Statement (Supplementary Material 1). (24) The study has been registered on ClinicalTrials.gov (NCT05489432).

Study setting

The intervention will be conducted in the KTCs' home environment, depending on their needs and preferences. Study visits will be conducted at the UMCG in the Netherlands at the following timepoints: baseline (T0), and at week 13 (T1) and week 26 (T2) after randomization.

Recruitment

Patients on the UMCG waiting list for kidney transplantation or waitlisted during the inclusion period, will be recruited by their treating physician and receive an information letter about the

risks and benefits of the study. Written informed consent will be obtained from the patient (Supplementary Material 2). Patient recruitment will start in January 2023 and end in June 2025.

Eligibility criteria

In order to be eligible to participate in this study, potential participants must meet all the following inclusion criteria:

1) Adult kidney transplant candidate (≥18 years).
2) Listed for kidney transplantation on the UMCG kidney transplant waiting list at the start of the study or waitlisted during the inclusion period (January 2023 – June 2025).

The exclusion criteria include:

1) Inability to read and/or speak the Dutch language.
2) Combined organ transplantation (e.g., kidney+pancreas, kidney+liver).
3) In case of living donor kidney transplant: a transplantation planned within 3 months.
4) Involved in a lifestyle intervention study.

Participant screening & assessment

After informed consent, participants will be screened for problems regarding physical activity, nutritional status or psychological wellbeing in an assessment.

To evaluate physical functioning, participants will complete several questionnaires, including the Duke Activity Status Index (DASI), the physical subscale of the Short Form 36 (SF-36) and the Short QUestionnaire to ASsess Health-enhancing physical activity (SQUASH). Additionally, participants will wear an activity tracker for three days and their handgrip-,

bicep- and quadricep strength will be measured. Furthermore, the Short Physical Performance Battery (SPPB) and the steep ramp test (SRT) will be performed.

To assess nutritional status, participants will complete the Patient-Generated Subjective Global Assessment Short Form (PG-SGA SF) and maintain a food diary for three days. In addition, the participant's hip-waist ratio and their Body Mass Index (BMI) will be measured. Lastly, a Bio-impedance analysis (BIA) will be conducted.

For the evaluation of psychological functioning, participants will be asked to complete the following questionnaires: State-Trait Anxiety Inventory (STAI6), Patient Health Questionnaire 9 (PHQ-9) and Checklist Individual Strength: subjective fatigue (CIS8R). Finally, the Montreal Cognitive Assessment will be administered.

To assess frailty status and health-related quality of life (HRQoL), each participant will complete the Tilbury Frailty Indicator (TFI) and the SF-36, respectively.

The details of the assessment are described in Table 1 and under *Outcome measurements*. Participants who present with one or more modifiable problem(s) will be eligible to take part in the intervention study. In this study, a modifiable problem is defined as a problem that can be altered by the means of prehabilitation.

Randomization and allocation concealment

All participants who present with at least one modifiable problem, as determined during the assessment at the baseline study visit, will be randomized to the intervention or control group on a 1:1 ratio using block randomization after stratification for sex and pre-emptive/non-pre-

emptive transplantation. This study will not be blinded as it is not possible to blind the participant, or healthcare professionals involved in the intervention. Randomization will take place using ALEA (www.aleaclinical.eu). The randomization will be performed by an independent researcher who is not involved in screening, recruitment, clinical care, or data collection.

Intervention

The home-based, multi-modal, tailor-made program will focus on three domains (physical activity, nutritional advice, and psychosocial support) depending on the preferences and needs of the participant. For each domain, interventions have been developed based on the behavioural change wheel (BCW) method. (16, 17) A context analysis was performed to gain insight into the problems KTCs face, and the factors (i.e., preferences, barriers, limitations and facilitating factors) that are important to them for the creation and implementation of a prehabilitation program. Two certified lifestyle coaches, a physiotherapist and a dietitian, will be involved in the intervention. The lifestyle coach, together with the participant and their significant other, will compose a personalized, goal-directed prehabilitation program that can be incorporated into the daily life of the participant. During the intervention, the lifestyle coach will provide (bi)weekly counselling sessions with the participant. In these sessions, the progress of the participant, including their goals, facilitators and barriers, will be discussed. Participants will be offered monthly counselling sessions after completing the maintenance program. Counselling ends when the participant chooses not to make use of the counselling sessions and/or when they undergo KT.

Physical activity

The aim of the physical activity interventions will be to improve the strength and endurance of KTCs. The criteria of The Nederlandse Norm Gezond Bewegen (NNGB, in English: Dutch Healthy Physical Activity Guidelines), which includes: 1) performing activities that are moderately intense in nature for at least 30 minutes a day/five days per week, and 2) performing activities to increase muscle strength for 20 minutes a day/ 2-3 days a week, will serve as guidance. (25) The intervention will differ per participant depending on his/her baseline fitness level, preferences and whether they are on dialysis. (26) Participants will receive a bag of weights (1-4 kilograms) and resistance bands (very light, light, medium, heavy), in order to perform lightweight and bodyweight exercises at home. Additionally, participants will be offered to participate in activities such as swimming, walking and cycling. Figure 2 shows the various components which will be considered whilst creating the tailor-made intervention for each participant.

Nutritional advice

Nutritional interventions will focus on improving nutritional status and body composition by supporting participants to engage in healthy and sustainable dietary habits. If participants already receive guidance from a dietician in the context of regular care, the nutritional advice will be coordinated with his/her dietician. The intervention will be tailored to the nutritional problems and/or dietary restrictions of each individual participant and focus on optimizing and preventing shortages or imbalances of energy, protein and/or other nutrients for all participants.

Psychosocial support

Psychosocial interventions will consist of individual coaching by a certified lifestyle coach during (bi)weekly counselling sessions. The sessions will focus on the use of

effective coping strategies, stress and energy management, and promoting social support. Significant others may take part in these sessions if the participant wishes that they do. In addition, interventions aimed at relaxation such as sleep hygiene and relaxation interventions (e.g., progressive muscle relaxation techniques, visual and auditory stimulation, breathing techniques) will be offered. Participants with clinically relevant scores regarding anxiety (STAI6 ≥12) or depression (PHQ-9 ≥10) will be referred to a social worker at their local hospital for further evaluation, treatment and/or referral to a psychologist. (27, 28)

Control group

The control group will receive care as usual. Standard medical care for KTCs consists of a consult with a nephrologist and/or nurse practitioner at their local hospital every three months approximately. In addition, a consult with a dietician is scheduled if laboratory values are not consistent with expected results from dietary restrictions for chronic kidney disease or upon demand of the KTC. Depending on the needs of the KTC a social worker can be consulted. Physical therapy consults may be advised by a nephrologist and/or nurse practitioner for those KTCs who experience declines in their fitness levels. The contents of the physical therapy session will depend on the fitness level of the KTC. Data on the use of allied healthcare will be collected. Regarding measurements, the same time intervals will be used in between assessments. A study visit at the UMCG will be planned at week 13 (T1) and week 26 (T2) after randomization.

Participant withdrawal

Participants may always withdraw from the study, without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons. Participants will be withdrawn if they get transplanted during the study.

If participants withdraw from the study prior to measurement point T1, new participants will be included to ensure sufficient power of the study. Participants who have withdrawn from the study after T1 but indicate that their data may be used in the follow-up studies (e.g., on the effect of prehabilitation on outcomes after transplantation) will be followed according to the specifications of the patient.

Outcome measurements

All outcome measurements are summarized in Table 1. The primary, secondary and clinical outcomes will be measured at three timepoints: T0 (baseline assessment), T1 (week 13) and T2 (week 26). If a participant is unable to make it to the study visit at week 13 or week 26, a study visit will be planned within a one-week time frame of these timepoints.

Primary outcome

The primary outcome will be change in frailty status between T0 and T1 as measured by the TFI. (29) This validated tool has been chosen as it covers multiple components of frailty. In addition, the sustainability of the intervention will be examined by change in frailty status between T1 and T2. The TFI is a multidimensional, validated questionnaire for measuring frailty among community dwelling older adults. (29) It consists of 15 items reflecting the different components of frailty: physical frailty (8 items), psychological frailty (4 items) and social frailty (3 items). The total TFI score ranges between 0-15. A score ≥5 is used as a cut-off point for frailty.

Secondary outcomes

Secondary endpoints include changes in physical functioning, nutritional status, psychological well-being and quality of life. To measure these changes, a set of questionnaires will be filled out prior to the study visits (T0/T1/T2) in the UMCG using an online survey. Participants who prefer a pen-and-paper survey, will receive one via mail. Physical tests will be done during the study visit at the UMCG.

Physical functioning will be measured by two questionnaires and five performance tests.

- The SQUASH will be used to gain insight into engagement in physical activities in one's daily life. (30)
- The DASI will be used to measure functional capacity. (31)
- An activity tracker will be used to measure the number of steps taken by the participant. Participants will be asked to wear the activity tracker for three days and note the steps per day in their food diary (see nutritional assessment).
- Handgrip strength will be assessed using the Jamar Hydraulic Hand Dynamometer (Patterson Medical JAMAR 5030J1, Warrenville, Canada). (32)
- Quadricep and bicep strength will be measured with a hand-held dynamometer CITEC CT 3002/30 handheld dynamometer (Haren, Netherlands). (33, 34)
- The SPPB will be used to measure physical performance regarding balance, gait speed and leg muscle strength. (35) The SPPB consists of a balance test, a 4-meter walking test and the 5 Times Sit-To-Stand test (5TSTS).
- The SRT will be performed on an electronically braked cycle ergometer to measure one's aerobic capacity. During the SRT, the resistive load is accelerated in a fast schedule (25 W/10 sec) until exhaustion of the participant. (36)

Nutritional status will be assessed by a questionnaire, a food diary, and three body measurements.

- The PG-SGA SF will be used to assess nutritional status across various domains: changes in body weight, changes in nutritional intake, symptoms which negatively influence intake, absorption and utilization of nutrients, and level of activities and function. (37)
- Participants will be asked to complete a food diary throughout consecutive three days, including one weekend day, to gather information on fat, protein, and energy intake.
- BMI will be calculated as follows: weight (in kg) divided by height (m) squared (kg/m^2).
- Hip and waist circumference will be measured in centimetres to calculate a waist-hip ratio.
- BIA will be conducted to non-invasively measure body composition (e.g., lean tissue index, fat tissue index, extra cellular and intra cellular volume) by using the InBodyS10.

Psychosocial well-being will be measured by three questionnaires.

- Symptoms of anxiety will be measured using the short-form of the STAI-6. (38)
- Symptoms of depression will be measured using the PHQ-9. (39)
- Fatigue will be measured using the CIS8R. (39)

Health-Related Quality of Life

To assess HRQoL, the SF-36 health survey will be used. It is a 36-item, self-reported questionnaire that captures participants' perceptions of their own health and wellbeing. Based on the item scores, a physical component score (PCS) and a mental component score (MCS) will be calculated. (40, 41)

Clinical outcomes

Clinical outcomes, including waitlist mortality, delisting, and the number of hospital admissions, will be assessed by medical record review until time of transplantation and recorded on a case record form.

Other measures

To gain insight into the capability, opportunity and motivation of participants to engage in behaviour change the following questionnaires and test will be administered at T0.

- Health literacy will be measured using the Dutch version of the Set of Brief Screening Questions (SBSQ). (42, 43)
- Barriers and motivators regarding physical activity will be measured using the Barriers and Motivators Questionnaire (BMQ). (44)
- Barriers and motivators regarding nutritional intake will be measured using a subset of the Motivators and Barriers to Health-Smart Behaviours Inventory regarding health food and healthy drinks. (45)
- Barriers and motivators regarding social support will be measured using the short version of the SSL-Interaction (SSL-I). (46)
- The Self-Efficacy to Manage Chronic Disease Scale (SE-MCDS) will be used to gain insight into the confidence of a person in the ability to successfully perform a specific task or behaviour related to one's health in various situations. (47, 48)
- Personal control will be measured using the Pearlin-Schooler Mastery Scale. (41, 48)
- To gain insight into goal directedness and action planning skills of participants, the Action and Coping planning questionnaire developed by Sniehotta et al. will be used. (49)

- MoCA will be used a screening tool for cognitive deterioration. (50)

Tertiary outcomes

Data regarding feasibility and acceptability of the prehabilitation program will be collected throughout the study period. To assess feasibility the following data will be collected:

- Enrolment (number of eligible participants, consent rate, reasons for refusal (if known))
- Attrition (percentage of completion of the program, reasons for drop-out)
- Fidelity (adherence to the program, barriers and facilitators; adjustments to the program)
- Safety (number of adverse events)
- Logistical problems

The acceptability of the prehabilitation program will be assessed among participants using the Treatment Acceptability and Preference (TAP) questionnaire and among involved healthcare professionals using the NoMAD questionnaire. (51, 52, 53) In addition, satisfaction, feedback regarding the program, barriers and facilitators for further implementation will be obtained by six focus group meetings with participants of the intervention group and involved healthcare providers at the end of the study period. The focus group meetings will be led by an experienced senior researcher.

Demographic and patient characteristics will be recorded throughout the study.

Sample size calculation

An a priori sample-size calculation was performed based on an effect size of 0.5, which is generally found across outcomes and across populations as indicative of a minimal clinically important difference. To find a statistically significant difference between the control and intervention groups in the change of frailty at the end of the prehabilitation program (T1) with a medium effect size (0.5), alpha-value of 0.05 (2-sided) and a power of 0.80 at least 128

participants are needed in the study, n = 64 in each group. Based on a drop-out rate of 15%, 148 KTCs will be needed for randomization. Given the estimated exclusion after the assessment of participants with no problems of 15%, 176 KTCs need to be included for assessment.

Based on a conservative estimation of 50% regarding response rate to the invitation to participate in the study, and an initial exclusion of 10% of the target population (e.g., because of a language barrier), a total of 388 KTCs (2x 176 needed for assessment + 10% exclusion) will be needed as potential eligible participants.

Statistical analysis

All analyses will be performed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, version 28.0. IBM Corp., Armonk, NY, USA). The analyses will be based on the intention-to-treat principal. A two-sided p-value of <0.05 will be considered to indicate statistical significance for all analyses.

An intention to treat analysis will be carried out to study the difference in outcome measures between the intervention and the control group. The primary outcome will be the change in frailty status between T0 and T1. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data.

Regarding missing data, imputation by mean or modus will be done if missing at random (MAR) is less than 5%. If MAR >5%, multiple imputation will be utilized. Imputation will not be performed if missing data are not random.

Explorative analysis will be performed to gain insight into differences between the intervention and the control group regarding changes in frailty status (T1-T2), physical functioning, nutritional status, psychosocial well-being, quality of life and clinical outcomes at the various measurement points. These changes will be analysed using the appropriate tests based on measurement level and distribution. Differences in proportions between groups will be examined using Chi-square tests. Differences between groups will be performed using the Students T-test or Mann-Whitney U-test depending on normality of data. Differences within groups will be tested with a paired-samples T-test or Wilcoxon signed-rank test depending on normality of data. Changes over time between T0- T2 will be analysed using General Linear Models analysis with group*time interaction.

Data regarding feasibility, acceptability and barriers and facilitators for further implementation (e.g., enrolment, attrition, adherence, safety, logistical problems) will be described using descriptive statistics.

Qualitative data from the focus group meetings will be audio recorded and transcribed verbatim. Transcriptions will be imported into Atlas.ti 22 (Scientific Software development GmbH, Berlin, Germany). Data will be iteratively analysed and discussed using six analysis steps: familiarization with the data, generation of initial codes, searching for themes, reviewing themes, defining and naming themes, and writing the report. (54, 55)

Data management

Data will be handled in accordance with the General Data Protection Regulation (GDPR) and the Dutch Act on Implementation of the General Data Protection Regulation (UAVG). All

participant data will be pseudonymized. Data collection forms will be stored in RoQua and REDCap. A key list (identification list) will be kept to be able to link data of the electronic patient dossier to a pseudonymized patient. This key list will be secured by a password and saved on a locked research drive. Hardcopy research data of the project will be stored in a locked filing cabinet in the office of the principal investigator, which will also be locked. The principal investigator will have access to the final trial dataset. After the completion of the research project, as soon as all research data have been analysed and processed, all hardcopy research documents will be sent to the central archive of the UMCG.

Data monitoring

The principal investigator has deemed the implementation of a data monitoring committee unnecessary due to the low-risk nature of this study.

Remuneration

Participants will not receive remuneration for their contribution to this study. However, they will receive reimbursement for the cost of travel and parking costs.

Patient and public involvement

The patient advisory committee (PAC) of the UMCG Transplant Center was involved in the process of development of the study by exchanging ideas and giving feedback on the research proposal. The patient council of the Dutch Kidney Foundation contributed to the acceptance of the grant that helped fund this study. Also, a context analysis was performed to gain insight into the problems that KTCs face and the help that they receive prior to transplantation.

The project's steering committee consists of patients, including a representative of the PAC of the Transplant Center, and professionals. This group discusses the progress of the study quarterly. Patients will be involved in further development of the prehabilitation program.

ETHICS AND DISSEMINATION

Medical ethical approval for this study has been granted Institutional Review Board of the UMCG (registration no. METc 2022/421). The study will adhere to institutional policies, local laws and the Declaration of Helsinki. Written informed consent will be obtained from all participants by their treating physician. Important protocol modifications will be communicated to relevant parties.

Although the risk of injury during exercise is negligible, this will be monitored weekly by a lifestyle coach. All adverse events will be followed until they have abated, or until a stable situation has been reached.

The results will be disseminated at international conferences and in peer-reviewed journals.

Contributors

The protocol was designed and written by CA and EEQ. It was critically reviewed by AH, YV, HM, SB, AR, SJLB, EF and RAP. All authors approved the final version of this manuscript.

Roles and responsibilities

Principal investigator: design and conduct of PreCareTx; preparation of protocol and revisions; preparation of investigators brochures and case report forms; organising steering committee meetings; publication of study reports.

PhD student: recruitment of patients; coordinating and supervising research students and lifestyle coaches; performing data analysis.

Steering committee: reviewing progress of the study; agreement of final protocol.

Funding

This work was supported by The Dutch Kidney Foundation, grant number 20OS008. This funding source had no role in the design of this study, nor will it have any role during its execution.

Trial sponsor

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Competing interests

The authors declare no competing interests.

Protocol version

Issue date: 13 February 2023, version 1.0.

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FIGURE TITLES

Figure 1. Overview PreCareTx study

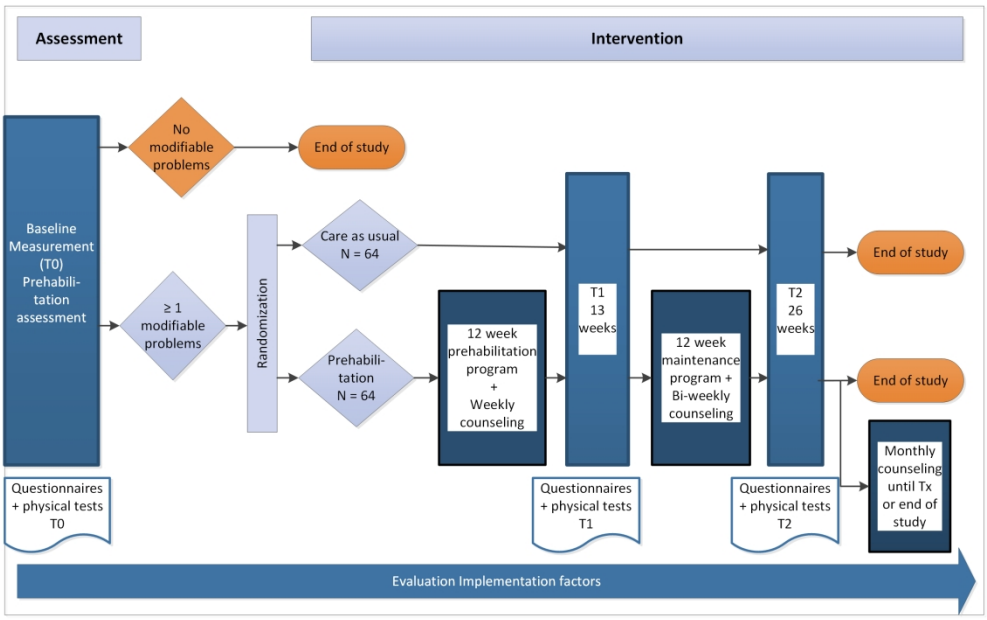
Figure 2. Components of the physical activity intervention and examples of possible activities

TABLES

Table 1. Overview of questionnaires and measurements at various measurement points

	Baseline (T0)	**Week 13 (T1)**	**Week 26 (T2)**
Measurements at home			
• Food diary (3 days)	x	x	x
• Activity tracker (3 days)	x	x	x
Questionnaires (online or paper-and pencil)			
Physical activity • Duke Activity Status Index (DASI)	X	X	X
Nutritional status • Patient-Generated Subjective Global assessment (PG-SGA- SF)	X	X	X
Psychological fitness • State-Trait Anxiety Inventory (STAI-6) • Patient Health Questionnaire (PHQ-9) • Checklist Individual Strength (CIS-8)	X X X	X X X	X X X
Outcomes • HRQoL- SF36	X	X	X
Questionnaires Com-B model			
Capability • *Capability* • Health Literacy (SBSQ-D) • *Physical ability* • Physical subscale SF36 • Duke Activity Status Index (DASI)	X (X) (X)		
Opportunity • *Social influences* • Social support (SSL-I) • *Environmental context and resources* • Barriers and motivators questionnaire • Health-Smart behaviour inventory	 X X X		
Motivation • *Beliefs about capabilities*			

• Self-efficacy (SE-MCDS) • Personal control (Mastery Scale) • *Goals & Planning* • Action planning and control planning questionnaire	X X X		
Tests and questionnaires during study visit			
Physical activity • Handgrip strength • Biceps strength • Quadriceps strength • Short Physical Performance Battery • Steep ramp test • Short Questionnaire to assess health-enhancing physical activity (SQUASH)	 X X X X X X	 X X X X X X	 X X X X X X
Nutritional status • Bio-impedance analysis (BIA) • BMI (height & weight measurement) • Hip-waist ratio	 X X X	 X X X	 X X X
Cognitive ability • Montreal Cognitive Assessment	 X		
Outcomes • Tilburg Frailty Indicator	 x	 x	 x



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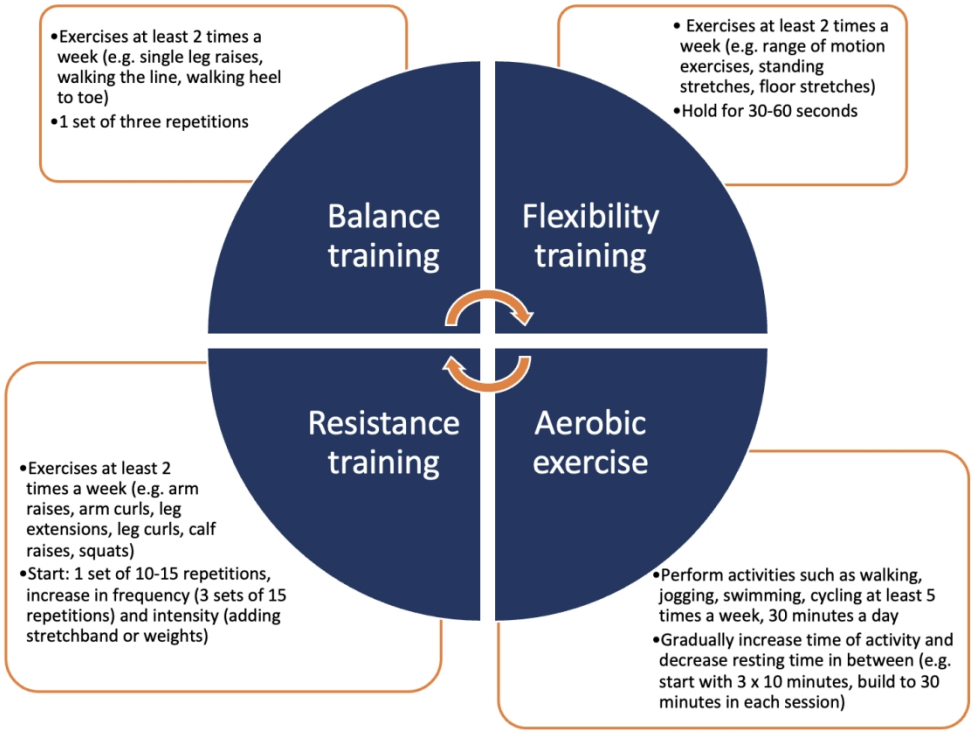

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SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1, line 1-3)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (page 3, line 5)
	2b	All items from the World Health Organization Trial Registration Data Set (N/A)
Protocol version	3	Date and version identifier (page 23, line 1-2)
Funding	4	Sources and types of financial, material, and other support (page 22, line 14-17)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (page 1, lines 4-17; page 22, line 1-4)
	5b	Name and contact information for the trial sponsor (page 22, lines 19-21)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (page 22, lines 14-17)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (page 22, lines 6-12).
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (page 5, line 21-25; page 6, line 1-19)
	6b	Explanation for choice of comparators (page 6, line 18-19)

Objectives	7	Specific objectives or hypotheses (page 6, line 20-24; page 7, line 1-7)
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (page 7, line 9-11)

Methods: Participants, interventions, and outcomes

Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 7, line 17-19)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (page 8, line 4-19)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (page 10, line 11-25; page 11-12)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (page 12, line 22-24)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (page 10, line 21-25)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (page 8, line 19)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (page 13, line 7-25; page 14-17)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (Figure 1)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (page 17, line 17-23; page 1-7)

Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 7, line 22-24)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 10, line 6-7)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (page 10, line 5-6)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 10, line 7-9)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (N/A; page 10, line 5-6)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (N/A)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (page 13-17; page 19, line 25)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (page 13, line 1-5)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (page 20, line 1-7)

Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (page 18, line 15-20)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (page 19, line 1-20)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (page 18, line 22-24)
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (page 20, line 9-11)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (N/A)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (page 21, line 8-10)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (N/A)
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (page 21, line 1-3)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (page 21, line 5-6)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 21, line 4-5)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (N/A)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (page 20, line 1-7)

Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 22, line 3-4)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (page 20, line 4-5)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (N/A)
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (page 21, line 12)
	31b	Authorship eligibility guidelines and any intended use of professional writers (N/A)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (N/A)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates (Supplementary Material 2)
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (N/A)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

Proefpersoneninformatie voor deelname aan medisch-wetenschappelijk onderzoek

Prehabilitatie voor niertransplantie kandidaten

PREhabilitation of CAndidates for REnal Transplantation (PreCareTx): A Hybrid Study

Inleiding

Geachte heer/mevrouw,

Met deze informatiebrief willen we u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u op de wachtlijst staat voor een niertransplantatie in het Universitair Medisch Centrum Groningen (UMCG). U leest hier om wat voor onderzoek het gaat, wat het voor u betekent, en wat de voordelen en nadelen zijn. Het is veel informatie. Wilt u de informatie doorlezen en beslissen of u wilt meedoen? Als u wilt meedoen, kunt u het formulier invullen dat u vindt in bijlage C.

Stel uw vragen

U kunt uw beslissing nemen met de informatie die u in deze informatiebrief vindt. Daarnaast raden we u aan om dit te doen:

- Stel vragen aan de onderzoeker die u deze informatie geeft.
- Praat met uw partner, familie of vrienden over dit onderzoek.
- Stel vragen aan de onafhankelijk deskundige, dr. A. van Beek .
- Lees de informatie op. www.rijksoverheid.nl/mensenonderzoek"

1. Algemene informatie

Het UMCG heeft dit onderzoek opgezet. Hieronder noemen we het UMCG steeds de ‘opdrachtgever’. Onderzoekers voeren het onderzoek uit in het UMCG.

De medisch-ethische toetsingscommissie van het UMCG heeft dit onderzoek goedgekeurd.

2. Wat is het doel van het onderzoek?

Het doel van dit onderzoek is na te gaan wat het effect van een prehabilitatie programma is op de algehele conditie van patiënten die op de wachtlijst staan voor een niertransplantatie. Prehabilitatie is een soort revalidatie maar dan voorafgaand aan een operatie. Het doel van prehabilitatie is door veranderingen in leefstijl de conditie van mensen die een operatie moeten ondergaan te verbeteren. Dit betreft zowel de lichamelijk conditie als het geestelijk welzijn. Prehabilitatie bestaat vaak uit verschillende onderdelen, zoals beweegactiviteiten, voedingsadviezen en omgaan met stress of vermoeidheid. Het programma wordt ‘op maat’ aangeboden zodat het aansluit bij de behoeften en mogelijkheden van u als

deelnemer. Het effect van het prehabilitatie programma vergelijken we met de zorg zoals die gebruikelijk gegeven wordt. De resultaten van dit onderzoek worden gepubliceerd in een medisch blad.

3. Wat is de achtergrond van het onderzoek?

Voor patiënten die op de wachtlijst staan voor een niertransplantatie is het van belang om, zowel lichamelijk als geestelijk, in een zo goed mogelijke conditie te zijn voor de transplantatie. De conditie van nierpatiënten is vaak verminderd door de chronische nieraandoening, door nevenaandoeningen en door de dialyse. Uit gegevens van de TransplantLines studie van het UMCG blijkt dat zo'n 90% van de niertransplantatiekandidaten één of meerdere problemen ervaart op het gebied van bewegen, voedingstoestand, vermoeidheid en/of stress.

Prehabilitatie is een programma dat u volgt om uw conditie te verbeteren. Hierdoor kan uw algehele conditie voor de transplantatie verbeteren, maar mogelijk verloopt hierdoor ook het herstel na de transplantatie sneller. Tot nu toe hebben drie onderzoeken laten zien dat de conditie van nierpatiënten verbeterd kan worden met prehabilitatie. In deze onderzoeken is aangetoond dat het volgen van het programma veilig was en dat deelnemers zich fitter voelden, meer energie en een betere conditie hadden, en dat het behulpzaam was bij het voorbereiden op de transplantatie. In deze onderzoeken werden alleen de gevolgen van een beweeg oefenprogramma onderzocht. Ook was het aantal patiënten dat betrokken was bij deze onderzoeken laag (18-37 deelnemers). Daarom willen we in dit onderzoek nagaan wat de effecten zijn van een op maat gemaakt prehabilitatie programma, waarin aandacht wordt besteed aan bewegen, voeding en/of omgaan met de mogelijke gevolgen van het leven met en nierziekte zoals stress of vermoeidheid.

4. Hoe verloopt het onderzoek?

Hoelang duurt het onderzoek?

Doet u mee met het onderzoek? Dan duurt dat in totaal ongeveer 26 weken.

Stap 1: bent u geschikt om mee te doen?

We willen eerst weten of u geschikt bent om mee te doen. Daarom doet de onderzoeker een aantal metingen:

- Voorafgaand aan het geschiktheidsonderzoek in het UMCG vragen we u om drie dagen een dieet dagboekje en het aantal stappen dat u loopt bij te houden. Hiervoor krijgt u een dagboekje en stappenteller thuis gestuurd. Het invullen vraagt ongeveer 15 minuten van uw tijd per dag.
- Voorafgaand aan het geschiktheidsonderzoek in het UMCG vult u een vragenlijst in met vragen over onder andere bewegen, voeding, vermoeidheid, stress en kwaliteit van leven. De vragenlijsten worden toegestuurd via e-mail of in een papieren versie als u dat liever hebt. Het invullen van de vragenlijst duurt ongeveer 60 minuten.
- Tijdens de studie visite in het UMCG wordt uw lichamelijke conditie gemeten met testen zoals een loop- en een fietstest en testen om de kracht in uw handen, armen en benen te meten. Uw voedingstoestand wordt vastgesteld door uw gewicht en lengte te meten en door uw

lichaamssamenstelling te meten met een bio-impedantie analyse. Deze metingen duren ongeveer een uur.

Als uit het geschiktheidsonderzoek blijkt dat u één of meerdere problemen heeft op het gebied van bewegen, voeding of geestelijk welzijn dan komt u in aanmerking voor prehabilitatie. Als er geen problemen worden vastgesteld dan stopt voor u het onderzoek.

Stap 2

Voor het onderzoek maken we 2 groepen:

- Groep 1: interventie groep. De mensen in deze groep ontvangen prehabilitatie naast de gebruikelijk zorg van hun eigen hulpverlener(s)
- Groep 2: controle groep. De mensen in deze groep ontvangen de gebruikelijke zorg van hun eigen hulpverlener(s).

Loting bepaalt in welke groep u komt. U heeft 50% kans om in de interventie groep en 50% kans om in de controle groep terecht te komen.

Stap 3: onderzoeken en metingen

Voor het onderzoek is het nodig dat u nog twee keer naar het UMCG komt. Dit is 13 weken en 26 weken na de loting. De bezoeken aan het UMCG duren ongeveer een uur per keer. We doen de volgende metingen:

- Voorafgaand aan de bezoeken in het UMCG vragen we u om drie dagen een dieet dagboekje en het aantal stappen dat u loopt bij te houden. Hiervoor krijgt u een dagboekje en stappenteller thuis gestuurd. Dit vraagt ongeveer 15 minuten van uw tijd per dag.
- Voorafgaand aan de bezoeken in het UMCG vult u een vragenlijst in met vragen over onder andere bewegen, voeding, vermoeidheid, stress en kwaliteit van leven. De vragenlijsten worden toegestuurd via e-mail of in een papieren versie als u dat liever hebt. Dit vraagt ongeveer 30 minuten van uw tijd per keer.
- Tijdens de studie visite in het UMCG wordt uw lichamelijke conditie weer gemeten met dezelfde testen als bij de eerste meting. Dit zijn testen om zoals een loop- en een fietstest en testen om de kracht in uw handen, armen en benen te meten. Uw voedingstoestand wordt vastgesteld door uw gewicht en lengte te meten en door uw lichaamssamenstelling te meten met een bio-impedantie analyse. Hierin wordt, via elektroden op uw handen en voeten, met een zwakstroom signaal de weerstand in uw lichaam gemeten. Dit duurt enkele seconden en u merkt daar niets van.
- De bezoeken aan het UMCG duren ongeveer een uur per keer.

In bijlage B staat een overzicht van de metingen in het onderzoek beschreven.

Interventiegroep

De groep die de prehabilitatie interventie krijgt (Groep 1) heeft naast de metingen drie gesprekken met een leefstijlcoach. Als u wilt mag u uw partner of een ander persoon die belangrijk voor u is meenemen. In het gesprek met de leefstijlcoach worden de resultaten van de onderzoeken besproken en samen met u een prehabilitatie programma opgesteld. Dit programma kan verschillende interventies omvatten zoals

beweegoefeningen, werken aan een goede voedingstoestand en/of leren omgaan met vermoeidheid. Wat het programma voor u in gaat houden wordt afgestemd op uw persoonlijke situatie. De afspraken met de leefstijlcoach worden gecombineerd met de afspraak voor de metingen in het UMCG. Deze afspraken duren ongeveer een uur. Voor de eerste afspraak met de leefstijlcoach moet u wel extra naar het UMCG komen. Tijdens het volgen van het prehabilitatie programma, krijgt u begeleiding van een leefstijlcoach. Hiervoor wordt elke week een telefonisch overleg ingepland van ongeveer 15 minuten.

Na het afronden van het prehabilitatie programma, vragen we u om deel te nemen aan een afsluitend groepsinterview met andere deelnemers. Deelname aan het groepsinterview is vrijwillig. Dit interview duurt ongeveer een uur en zal digitaal gehouden worden. Het doel van dit interview is nagaan welke onderdelen van het prehabilitatie programma nog verbeterd kunnen worden. Voorafgaand aan het groepsinterview vragen we u om een vragenlijst in te vullen over uw ervaringen met het prehabilitatie programma.

Controle groep
Als u wordt ingeloot in de controle groep (groep 2) ontvangt de gebruikelijk zorg van uw nefroloog of verpleegkundig specialist. Als een diëtist of medisch maatschappelijk werker bij uw zorg betrokken is dan gaat ook deze zorg door zoals u dat gewend bent. U ontvangt wel de uitslagen van de vragenlijsten en lichamelijke testen die op de verschillende meetmomenten gedaan worden voor het onderzoek.

Wat is er anders dan bij gewone zorg?
Zowel in de controle groep als de interventie groep verandert er niets aan de gebruikelijk zorg. De afspraken die u bij uw arts of verpleegkundig specialist heeft voor de controle van uw nierziekte gaan gewoon door. Wel moet u drie keer (controle groep) of vier keer (interventie groep) naar het UMCG komen voor de metingen die bij het onderzoek horen. Voor de interventiegroep zijn de drie gesprekken met de leefstijlcoach en de wekelijkse begeleiding van de leefstijlcoach extra bovenop de gebruikelijke zorg.

Belangrijk voor u om te weten is dat deelname aan dit onderzoek niet van invloed is op uw transplantatie. Als u tijdens het onderzoek een oproep ontvangt voor een transplantatie dan kan deze gewoon plaatsvinden maar stopt voor u dit onderzoek.

5. Welke afspraken maken we met u?

We willen graag dat het onderzoek goed verloopt. Daarom maken we de volgende afspraken met u:

- U vult de vragenlijsten en voedingsdagboekjes in;
- U draagt een stappenteller zoals afgesproken;
- U komt naar iedere afspraak;
- U volgt het prehabilitatie programma op de manier die u met de leefstijlcoach afgesproken heeft;
- U doet niet mee aan een ander medisch-wetenschappelijk onderzoek gericht op leefstijlverandering;
- U neemt contact op met de onderzoeker in deze situaties:
    - U krijgt plotseling problemen met uw gezondheid;
    - U wilt niet meer meedoen met het onderzoek;

- U krijgt een niertransplantatie tijdens het onderzoek.

6. Van welke bijwerkingen, nadelige effecten of ongemakken kunt u last krijgen?

De risico's van deelname aan het onderzoek zijn klein. Uit eerder onderzoek bij patiënten die op de wachtlijst staan voor een orgaantransplantatie is gebleken dat prehabilitatie veilig is.

7. Wat zijn de voordelen en de nadelen als u meedoet aan het onderzoek?

Meedoen aan het onderzoek kan voordelen en nadelen hebben. Hieronder zetten we ze op een rij. Denk hier goed over na, en praat erover met anderen.

Voordelen van meedoen aan het onderzoek kunnen zijn:

- U krijgt inzicht in hoe uw conditie is;
- De interventie kan uw algehele conditie verbeteren, maar zeker is dat niet.

Nadelen van meedoen aan het onderzoek kunnen zijn:

- Mogelijke ongemakken van de oefeningen, zoals spierpijn, in het onderzoek.

Deelname aan het onderzoek betekent ook:

- Dat u extra tijd kwijt bent;
- (Extra) testen;
- Dat u afspraken heeft waaraan u zich moet houden;

Al deze zaken zijn hiervoor onder punt 4, 5 en 6 beschreven.

Wilt u niet meedoen?

U beslist zelf of u meedoet aan het onderzoek. Meedoen is vrijwillig. Wilt u niet meedoen? Dan verandert er niets, u krijgt de gebruikelijke zorg voor uw nierziekte.

8. Wanneer stopt het onderzoek?

De onderzoeker laat het weten als er nieuwe informatie over het onderzoek komt die belangrijk voor u is. De onderzoeker vraagt daarna of u blijft meedoen.

In deze situaties stopt voor u het onderzoek:

- Alle onderzoeken volgens het schema zijn gedaan;
- Het einde van het hele onderzoek is bereikt;
- Als u tijdens de onderzoeksperiode een niertransplantatie ondergaat;
- U wilt zelf stoppen met het onderzoek. Dat mag op ieder moment. Meld dit dan meteen bij de onderzoeker. U hoeft niet te vertellen waarom u stopt. U krijgt dan weer de gebruikelijke behandeling voor uw nierziekte. De onderzoeker zal u nog wel uitnodigen voor een nacontrole;

- De onderzoeker vindt het beter voor u om te stoppen. De onderzoeker zal u nog wel uitnodigen voor een nacontrole;
- Een van de volgende instanties besluit dat het onderzoek moet stoppen:
    - De overheid;
    - De medisch-ethische commissie die het onderzoek beoordeelt.

Wat gebeurt er als u stopt met het onderzoek?
De onderzoekers gebruiken de gegevens die tot het moment van stoppen zijn verzameld.

9. Wat gebeurt er na het onderzoek?

Krijgt u de resultaten van het onderzoek?
Het onderzoek loopt tot september 2025. Daarna laat de onderzoeker u weten wat de belangrijkste uitkomsten zijn van het onderzoek. Tot die tijd wordt u geïnformeerd over de voortgang van het onderzoek in een nieuwsbrief.

10. Wat doen we met uw gegevens?

Doet u mee met het onderzoek? Dan geeft u ook toestemming om uw gegevens te verzamelen, gebruiken en bewaren.

Welke gegevens bewaren we?
We bewaren deze gegevens:
- uw naam;
- uw geslacht;
- uw adres;
- uw leeftijd;
- gegevens over uw gezondheid;
- (medische) gegevens die we tijdens het onderzoek verzamelen.

Waarom verzamelen, gebruiken en bewaren we uw gegevens?
We verzamelen, gebruiken en bewaren uw gegevens om de vragen van dit onderzoek te kunnen beantwoorden. En om de resultaten te kunnen publiceren in een medisch tijdschrift.

Hoe beschermen we uw privacy?
Om uw privacy te beschermen geven wij uw gegevens een code. Op al uw gegevens zetten we alleen deze code. De sleutel van de code bewaren we op een beveiligde plek in het ziekenhuis. Als we uw gegevens verwerken, gebruiken we steeds alleen die code. Ook in rapporten en publicaties over het onderzoek kan niemand terughalen dat het over u ging.

Wie kunnen uw gegevens zien?

Sommige personen kunnen wel uw naam en andere persoonlijke gegevens zonder code inzien. Dit kunnen gegevens zijn die speciaal voor dit onderzoek zijn verzameld, maar ook gegevens uit uw medisch dossier. Dit zijn mensen die controleren of de onderzoekers het onderzoek goed en betrouwbaar uitvoeren. Deze personen kunnen bij uw gegevens komen:

- Een controleur die voor de onderzoeker werkt;

Deze personen houden uw gegevens geheim. Wij vragen u voor deze inzage toestemming te geven. De Inspectie Gezondheidszorg en Jeugd kan zonder uw toestemming uw gegevens inzien.

Hoelang bewaren we uw gegevens en lichaamsmateriaal?
We bewaren uw gegevens 15 jaar in het ziekenhuis.

Mogen we uw gegevens gebruiken voor ander onderzoek?
Uw gegevens kunnen na afloop van dit onderzoek ook van belang zijn voor ander wetenschappelijk onderzoek op het gebied van niertransplantatie. Als u meedoet aan het TransplantLines onderzoek van het UMCG worden uw gegevens van de vragenlijst ook daarvoor gebruikt. Dan hoeft u deze vragenlijsten niet nog een keer in te vullen. In het toestemmingformulier geeft u aan of u dit goed vindt. Geeft u geen toestemming? Dan kunt u nog steeds meedoen met dit onderzoek maar worden uw gegevens niet gekoppeld aan het TransplantLines onderzoek. U krijgt dezelfde zorg.

Wat gebeurt er bij onverwachte ontdekkingen?
Tijdens het onderzoek kunnen we toevallig iets vinden dat belangrijk is voor uw gezondheid. De onderzoeker neemt dan contact op met uw medisch specialist. U bespreekt dan met uw specialist wat er moet gebeuren. U geeft met het formulier toestemming voor het informeren van uw specialist.

Kunt u uw toestemming voor het gebruik van uw gegevens weer intrekken?
U kunt uw toestemming voor het gebruik van uw gegevens op ieder moment intrekken. Maar let op: trekt u uw toestemming in, en hebben onderzoekers dan al gegevens verzameld voor een onderzoek? Dan mogen zij deze gegevens nog wel gebruiken.

Wilt u meer weten over uw privacy?

- Wilt u meer weten over uw rechten bij de verwerking van persoonsgegevens? Kijk dan op www.autoriteitpersoonsgegevens.nl
- Heeft u vragen over uw rechten? Of heeft u een klacht over de verwerking van uw persoonsgegevens? Neem dan contact op met degene die verantwoordelijk is voor de verwerking van uw persoonsgegevens. Voor uw onderzoek is dat:
    - Avril Haanstra, UMCG. Zie bijlage A voor contactgegevens.
- Als u klachten heeft over de verwerking van uw persoonsgegevens, raden we u aan om deze eerst te bespreken met het onderzoeksteam. U kunt ook naar de Functionaris Gegevensbescherming van het UMCG gaan. In bijlage A staat waar u die kunt vinden. Of u dient een klacht in bij de Autoriteit Persoonsgegevens.

Waar vindt u meer informatie over het onderzoek?
Op de volgende website(s) vindt u meer informatie over het onderzoek:www.ClinicalTrials.gov. Na het onderzoek kan de website een samenvatting van de resultaten van dit onderzoek tonen. U vindt het onderzoek door te zoeken op NCT05489432.

11. Krijgt u een vergoeding als u meedoet aan het onderzoek?

De extra testen voor het onderzoek kosten u niets. U krijgt ook geen vergoeding als u meedoet aan dit onderzoek. Wel krijgt u een vergoeding voor uw (extra) reiskosten (€ 0.19/km en parkeerkosten).

12. Bent u verzekerd tijdens het onderzoek?

U bent niet extra verzekerd voor dit onderzoek. Want meedoen aan het onderzoek heeft geen extra risico's. Daarom hoeft de onderzoeker van de METc geen extra verzekering af te sluiten

13. We informeren uw behandelend specialist

De onderzoeker stuurt uw behandelend specialist een brief om te laten weten dat u meedoet aan het onderzoek. Dit is voor uw eigen veiligheid.

14. Heeft u vragen?

Vragen over het onderzoek kunt u stellen aan de onderzoeker. Wilt u advies van iemand die er geen belang bij heeft? Neem dan contact op met dr. A.P. van Beek. Hij weet veel over het onderzoek, maar werkt niet mee aan dit onderzoek.
Heeft u een klacht? Bespreek dit dan met de onderzoeker of de arts die u behandelt. Wilt u dit liever niet? Ga dan naar klachtencommissie van uw ziekenhuis. In bijlage A staat waar u die kunt vinden.

15. Hoe geeft u toestemming voor het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Daarna vertelt u de onderzoeker of u de informatie begrijpt en of u wel of niet wilt meedoen. Wilt u meedoen? Dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt. U en de onderzoeker krijgen allebei een getekende versie van deze toestemmingsverklaring.

Dank voor uw tijd.

16. Bijlagen bij deze informatie

A. Contactgegevens
B. Overzicht metingen
C. Toestemmingsformulier proefpersoon

Bijlage A: contactgegevens UMCG

Hoofd onderzoeker:
Dr. Coby Annema
Email: j.h.annema@umcg.nl
Tel: 050 361 1490
Bereikbaarheid: maandag-dinsdag-donderdag-vrijdag (9:00 – 17:00 uur)

Voor een eventueel 2de aanspreekpunt:
Drs. Avril Haanstra
Email: a.j.haanstra@umcg.nl
Tel: 06 2565 1034
Bereikbaarheid: maandag tot vrijdag (9:00 – 17:00 uur)

Onafhankelijk arts:
Dr. A.P. van Beek
Internist/ endocrinoloog
Email: a.p.van.beek@umcg.nl
Bereikbaarheid: maandag tot vrijdag (9:00 – 17:00 uur)

Klachten:
Wanneer u een klacht heeft over de gang van zaken omtrent het onderzoek, kunt u dit melden bij de hoofdonderzoeker. Indien u dat niet wilt, kunt u terecht bij de onafhankelijk klachtenfunctionaris via: (050) 361 22 20 (secretariaat) of klachtenfunctionaris@umcg.nl.

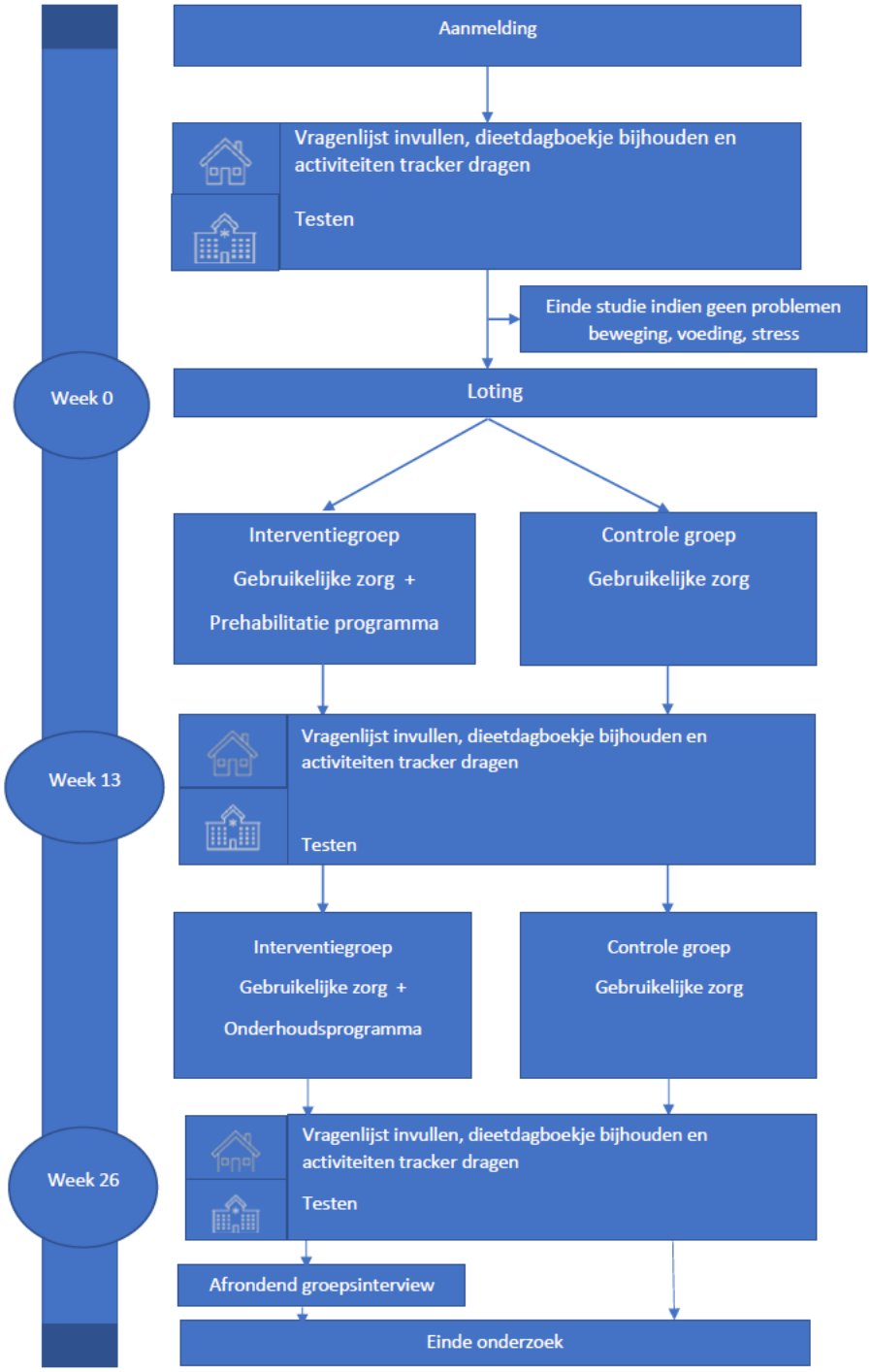
Wanneer u klachten heeft over de behandeling kunt u contact opnemen met het team Patiënten informatie via: (050) 361 33 00 of patienteninformatie@bvl.umcg.nl

De functionarissen voor de Gegevensbescherming van het UMCG zijn te bereiken via privacy@umcg.nl

Voor meer informatie over uw rechten: www.autoriteitpersoonsgegevens.nl

Bijlage B: Overzicht metingen

Hieronder vindt u een schematisch overzicht van het PreCareTx-onderzoek.



Bijlage C: toestemmingsformulier proefpersoon

Behorende bij

Prehabilitatie voor niertransplantiekandidaten (PreCareTx-onderzoek)

- Ik heb de informatiebrief gelezen. Ook kon ik vragen stellen. Mijn vragen zijn goed genoeg beantwoord. Ik had genoeg tijd om te beslissen of ik meedoe.
- Ik weet dat meedoen vrijwillig is. Ook weet ik dat ik op ieder moment kan beslissen om toch niet mee te doen met het onderzoek. Of om ermee te stoppen. Ik hoef dan niet te zeggen waarom ik wil stoppen.
- Ik geef de onderzoeker toestemming om mijn specialist te laten weten dat ik meedoe aan dit onderzoek.
- Ik geef de onderzoeker toestemming om mijn huisarts of specialist informatie te geven over onverwachte bevindingen uit het onderzoek die van belang zijn voor mijn gezondheid.
- Ik geef de onderzoekers toestemming om mijn gegevens te verzamelen en gebruiken. De onderzoekers doen dit alleen om de onderzoeksvraag van dit onderzoek te beantwoorden.
- Ik weet dat voor de controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief. Ik geef deze mensen toestemming om mijn gegevens in te zien voor deze controle.

- Wilt u in de tabel hieronder ja of nee aankruisen?

Ik geef toestemming om mijn gegevens te bewaren om dit te gebruiken voor ander onderzoek, zoals in de informatiebrief staat.	Ja ☐	Nee☐
Ik geef toestemming om mij eventueel na dit onderzoek te vragen of ik wil meedoen met een vervolgonderzoek.	Ja ☐	Nee☐

Ik wil meedoen aan dit onderzoek.

Mijn naam is (proefpersoon): ……..

Handtekening: …… Datum : __ / __ / __

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Wordt er tijdens het onderzoek informatie bekend die de toestemming van de proefpersoon kan beïnvloeden? Dan laat ik dit op tijd weten aan deze proefpersoon.

Naam onderzoeker (of diens vertegenwoordiger):……

Handtekening:…… Datum: __ / __ / __

De proefpersoon krijgt een volledige informatiebrief mee, samen met een getekende versie van het toestemmingsformulier.