Prehabilitation of elderly frail or pre-frail patients prior to elective surgery (PRAEP-GO): study protocol for a randomized, controlled, outcome-assessor blinded trial

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Research Article

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Abstract

Background

Frailty is accompanied with a reduced physical capacity, mobility, muscle strength and endurance. (Pre-)Frailty is present in an older surgical population in up to 50% with an increased risk for peri- and post-surgical complications. Consequently, these patients often suffer from a delayed or diminished recovery, loss of autonomy and quality of life, as well as a decrease of functional and cognitive capacity. As frailty is modifiable, we hypothesize that prehabilitation is able to improve the physiological reserves of surgical patients ≥ 70 years old and reduce the care dependency 12 months postoperatively.

Methods

Patients ≥ 70 years old scheduled for elective surgery or intervention will be investigated in this multicentre, randomized controlled study. We aim at including 1400 participants in our study with an allocation ratio of 1:1. The intervention consists of (1) a shared decision-making process with an interdisciplinary and interprofessional shared decision making conference as well as (2) a 3-week multimodal prehabilitation program including exercise therapy, nutritional intervention, mobility and balance training as well as psychosocial interventions and medical assessment. Frequency of the prehabilitation is 5 times / week for 3 weeks. The primary endpoint is defined as level of care dependency 12 months after surgery or intervention.

Discussion

Prehabilitation has been proven to be effective for different patient populations, including colorectal, transplant, and cardiac surgery, among other. In contrast, evidence for prehabilition in older, frail patients is not established yet. To the best of our knowledge, this is the largest study on prehabilitation for older people with frailty in a general elective surgery patient cohort.

Trial registration:

Clinical Trials. NCT04418271. Registered 5 June 2020, https://clinicaltrials.gov/ct2/show/NCT04418271), Universal Trial Number (UTN): U1111-1253-4820

Introduction

Due to the increasing life expectancy of the population and significant medical progress, more and more complex surgical interventions are performed in older patients. Even though severe postoperative complications like mortality have been reduced in the last decades [1], older patients are at risk to lose independence and to develop medium and long-term disabilities in the cognitive and functional domains [2–4]. Additionally, older patients show a higher risk for hospital-readmission associated with a delay in functional recovery [5]. These risks of postoperative complications are not only determined by pre-existing conditions like diabetes mellitus or cardiovascular disease [6–8], but also by the frailty syndrome [9–12].

Frailty is associated with restrictions in the functional reserve, including mobility, muscle strength and vital capacity. It is an independent risk factor for the development of postoperative complications such as postoperative delirium [13], overall mortality and long-term care [14], and long-term cognitive disorders [15]. The prevalence of frailty is estimated to be between 4.0% and 27.3% within the population ≥ 65 years [16]. In the perioperative setting, the prevalence is even higher, with up to 50%, depending on the surgical discipline and screening tool used [17].

Frail patients may benefit from prehabilitation, defined as a targeted, multiprofessional treatment of individual components of the frailty syndrome. Prehabilitation interventions are safe to perform [18, 19] and have demonstrated to result to a faster post-operative recovery of functional skills [20, 21], reduction of postoperative complications like cognitive disorders or a postoperative delirium [22–25], and shorter hospital stays [26]. However, most of these findings are restricted to specific patient groups or types of surgery with missing evidence in a general surgical population [27].

To evaluate the clinical and health-economic effectiveness of prehabilitation in elderly frail or pre-frail patients prior to elective surgery, we conduct a multicentre, randomized controlled outcome-assessor blinded trial, comparing the effectiveness of a prehabilitation program with standard care. All patients will be followed up for a year after surgery to determine the effects of the prehabilitation intervention on long-term care dependency as well as other outcomes on clinical and economic effectiveness.

Methods

Study design

This study is an assessor-blinded, two-arm parallel-group, randomized, controlled, multicentre trial (RCT) in frail or pre-frail patients before elective surgery in Germany with a follow-up of 12 months and an allocation ratio of 1:1 per hospital. The intervention group will receive prehabilitation in one of four different settings: 1) inpatient facilities like geriatric wards, 2) day clinics, 3) outpatient rehabilitation centres, or 4) home-based by a mobile rehabilitation team. A current list of participating centres and prehabilitation partners as well as the current version of the study protocol in German and English language (V1.1; Date: 6/13/2020) can be found online at https://www.praep-go.de. The flow diagram of the study is presented in Fig. 1, the SPIRIT Checklist is provided in Additional File 2.

Objectives and research questions

The objective of this RCT is to evaluate the effectiveness of a 3-week prehabilitation program for patients 70 years or older with frailty or pre-frailty before undergoing selective surgery.

Primary research question:

Can a shared decision-making conference and three-week prehabilitation program improve "care dependency" one year after surgery.

Secondary research questions:

1. Is the intervention of a of a shared decision-making conference and three-week prehabilitation program cost-effective?
2. What is the effect of a shared decision-making conference and three-week prehabilitation program on the following parameters within 12 months after surgery: (a) new diagnosis of neurocognitive disorder, (b) frequency of suspected neurocognitive disorder or dementia, (c) frailty, (d) polypharmacy, (e) alcohol use, (f) tobacco use, (g) sarcopenia, (h) nutritional status, (i) functional status, (j) depression, (k) anxiety, (l) health-related quality of life, (m) disability, (n) fear of falling, (o) incidence of falls, (p) social situation, (q) pain, (r) lonliness, (s) survival, (t) frequency of doctor visits in the follow-up period, (u) frequency and length of hospitalisations in the follow-up period.
3. What is the autonomic preference of patients concerning medical decisions and the extent of involvement of patients, relatives, or health-care professionals in shared-decision making?
4. What is the health-trajectory of patients 12 years after surgery with and without a shared decision-making conference and three-week prehabilitation program (diagnoses, medication, health-resource utilization)?

Additional research questions are explored in an accompanying research programme ANA-PRAEP-GO (NCT04880824) which also includes translational research questions.

Eligibility criteria

Inclusion criteria are: (1) age ≥ 70 years, (2) elective surgery/intervention procedure planned, (3) expected duration of anaesthesia > 60 minutes and (4) pre-frail or frail based on the frailty phenotype of Fried. For that purpose, muscle weakness, gait speed, subjective fatigue, weight loss and physical activity is assessed [28]. Measurements to identify these parameters include hand grip strength and gait speed over 15 ft. [29], self-reported weight loss of 4.5 kg or more within the last 12 months, self-reported fatigability within the last week as proposed by Fried et al (2001) [28]. For identifying low levels of physical activity, a metabolic equivalent of task (MET) of < 3 is used. MET of 3 is defined as moderate activity according to a guideline on activity recommendations in adults [30]. Patients are defined as pre-frail with at least one item indicated as positive and frail with three or more positive items.

Participation was initially limited to patients of one public health insurance provider *Barmer* due to legal reasons of the funding. We applied for permission to include all patients covered by statutory health insurance, which was granted in December 2020. Following that permission, we included patients from all statutory health insurance companies in Germany.

Exclusion criteria are: (1) severe cardiological condition (i.e., New York Heart Association (NYHA) grade IV), (2) severe pulmonal condition (Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade IV), (3) intracranial procedures, (4) palliative patients, (5) language barrier, (6) participation in another interventional trial not approved by the steering committee or another interventional rehabilitation trial, and 7) lack of consent to participate in the study.

Recruitment and screening

Patients are recruited during a preoperative visit to the surgical or anaesthesia department in each participating study centre. All eligible patients who are either frail or pre-frail based on the frailty screening will be invited to participate in our study by a study team physician. Information on duration and aims of the study, the role of each participant, randomization and any pre-identified risks will be explained in

written and oral form to each potential participant. Written consent to participate is mandatory before proceeding to any further study-related proceedings. Original patient information and consent form are provided in Additional File 3. Participants who agreed to participate in the study are further offered to participate in complementary studies designed to investigate specific research topics in the study population not covered by the grant of this study or including biological specimens. Participation in these complementary studies is not a prerequisite to participate in PRAEP-GO. All complementary topics are covered by additional study protocols, are registered as separate research projects in clinicaltrials.gov, and are subject to ethical approval.

Interventions

The control group will receive no intervention besides usual care as part of the surgery process and the rehabilitation following the surgery. For a pragmatic effectiveness analysis, the “usual care”-comparator seemed the appropriate option.

The intervention group will receive (1) a shared decision making (SDM) conference and (2) prehabilitation of three weeks before the elective surgery. The surgery-process of the patients will not be influenced, nor will study participation have any influence on post-surgery procedures, such as hospital stay or rehabilitation.

Shared Decision making (SDM) conference

SDM implies the involvement of the patient in clinical decision-making based on ethical considerations of informed decision making. Patients should be involved in their healthcare and make patient-centred decisions, i.e. decisions that best suit the individual preferences and needs of the patient rather than the preferences of the health care professional [31]. Barriers to participation in the SDM process were identified among older adults, including physical and mental limitations due to chronic conditions, but also difficulties in providing understandable and clear information about the disease and therapy to patients [32, 33].

Traditionally SDM is organized between a physician and the patient (sometimes together with a significant other), while newer approaches involve an interdisciplinary or interprofessional team 20795835. Such an interdisciplinary and interprofessional process has been adopted in PRAEP-GO.

The SDM process used in our study is based on the three-talks-model [34, 35]. The model consists of three phases (Choice Talk, Option Talk, and Decision Talk). In this study, these three phases will be conducted in different settings. The first phase (Choice Talk) will take place after the baseline visit and subsequent randomization. The assessor will prepare the patient about the coming phase 2, will identify his or her willingness to participate in the decision-making process and will discuss any needs and priorities that would influence the prehabilitation process. Patients can choose to participate together with a family member or any other person of trust. In the case of a limited (or no) willingness to participate in phase 2 of the SDM-process, the assessor will adopt a proxy role for the patient. Patient and assessor will discuss how the assessor can, in his or her role as proxy, comply with the patient’s needs and priorities.

Phase 2 of the SDM-process (Option Talk) is a multidisciplinary and multiprofessional case conference. Mandatory participants of this conference will be the assessor of the baseline visit, physicians from the fields of anaesthesiology, geriatrics, and the respective field of surgery or intervention, and either a therapist (physio- or occupational therapist) or a nurse. Additional participation of a general practitioner is encouraged. Participation at the conference is possible through personal attendance, telemedicine or by telephone. During the conference, different options on the optimal setting for the prehabilitation as well as individual and patient-centred goals of the prehabilitation will be discussed. These goals are categorized into strength-, endurance-, mobility-; activities of daily living (ADL), and nutritional-related interventions. Other goals can include psychosocial and neurocognitive interventions, speech therapy, reduction of polypharmacy, and others, based on the identified needs and goals of the patient. The goal of this conference is not to provide definite decisions but to lay out different realistic options, to hear the patient’s opinions (either through themselves or through their proxy) and to provide information for deriving a comprehensive prehabilitation plan to all members of the conference.

The third and final phase (Decision Talk) will again be conducted by the patient and the assessor. The objective of this phase is to define patient-centred goals for the prehabilitation period as well as to decide on the setting in which the prehabilitation will take place (in-house, day clinic, ambulatory, home-based). For the prehabilitation, one primary goal and two secondary goals are defined; an additional category of “other goals” is included to cover prehabilitation goals that do not fit in one of the former categories (see Table 1). The decision talk can be included in the case conference described above.

Prehabilitation

After completing the SDM process, all participants within the intervention group will receive a 3-week prehabilitation. All interventional sessions within the prehabilitation program will be performed by multiprofessional teams with formal training in their respective profession as well as special training in the defined prehabilitation program. During these three weeks of personalized prehabilitation, 30 sessions of multimodal

therapy intervention of 30 minutes each will be conducted in the setting selected in the SDM process. As part of the standardization of the intervention, the number of therapy sessions per week is defined based on the goals (primary, secondary, others) for each patient. There will be 10 supervised sessions per week that are performed twice daily on five days per week and the patient is encouraged to do six unsupervised sessions per week, resulting in a total of 45–48 exercise sessions over the course of the prehabilitation (see Table 1).

Table 1
Number of interventional sessions per week based on goals. S = supervised intervention; U = unsupervised intervention

Goals	Supervised		Unsupervised	
	Week 1	Week 2	Week 3	Week 1–3
Primary	5	5	5	2
Secondary 1	3	2	2	2
Secondary 2	1	1	1	1
Other	1	2	2	1
TOTAL	10	10	10	6

Exercises are planned based on the defined goals. All exercises are based on the recommendations on physical activity for older adults by the American college of sports medicine and the American heart association [36]: Aerobic exercises should be performed at least three non-consecutive days a week for a minimum of 20 minutes. Strengthening exercises are performed at least two non-consecutive times per week with a minimum of 8 to 10 exercises, so that each participant should be able to perform 10 to 15 repetitions on each exercise. All exercises are performed with a perceived subjective effort of at least 5 to 6 on a scale between 0 and 10 (0 defined as sitting, 10 as “all-out effort”) [36]. Exercises for increasing mobility and balance performance will be performed based on the Otago exercise program (OEP), that has consistently shown to reduce overall mortality and falls in older people [37]. In our study, the supervising physiotherapist or occupational therapist will teach and supervise the exercise components of the OEP as part of the interventional sessions, additional unsupervised exercises will be prescribed by the same therapist based on the progress of each participant over the course of the prehabilitation program.

The supervising physical therapist will adapt the performed exercises to comply with the exercise program recommendations over all sessions using a progression chart. The progression chart consists of an adapted version published by Gschwind and Pfenninger (2016) who developed an exercise program for fall prevention in Switzerland [38]. The underlying principle of this program is to define a basic exercise without any additional input which can be either assisted or exacerbated to de- and increase the difficulty as illustrated in Fig. 2. Assistance can be provided either by stabilizing the participant through holding at bars, a chair, or a wall, or through assistance by a therapist. Exacerbation can be achieved by change of body position, limiting sensory input (e.g., closed eyes), combined and complex or asymmetrical movements, disturbances of the movement patterns and, at the last stage, resistance training with weights, rubber bands, expanders, or other exercise equipment. Combining exercises with cognitive challenges will be used in mobility and balance training, and in ADL-training.

Adherence

Adherence is measured through the analysis of the documentation of the prehabilitation. Additionally, adherence to unsupervised exercises by the participants will be monitored by keeping a diary by all participants in the intervention group.

Outcome measures

The primary outcome is the level of care dependency 12 months after surgery. Care dependency is measured using the German structured assessment “Neues Begutachtungsinstrument” (NBA) [39]. The NBA is a standardized tool used by the medical service of the statutory health insurance companies in Germany to assess the need of professional help in care of older people or people with disabilities as well as the amount and type of care assistance needed. Results of the NBA are mandatory to get financial help from the national care insurance for professional care assistance. The NBA consists of six domains being assessed: (1) Mobility, (2) Cognitive and communication ability, (3) Behaviour and psychological problems, (4) Self-dependence, (5) Disease-specific demands and burdens, and (6) Daily routine scheduling and social contacts. Based on the NBA, six grades of care dependency are defined from zero (no dependency) to five (highest level of dependency) [40].

The following secondary outcome measures are defined:

1. Peri-surgical complications
2. *Post-surgical complications during hospital stay*, e.g. unplanned admission to intensive care unit (ICU), length of stay (LOS) in ICU, presence of delirium, mobilization speed and hospital LOS.

3. *Exercise adherence and composition during prehabilitation*. For this, the responsible therapists will document all exercise and therapy sessions. Additionally, patients will fill out a training diary to document all unsupervised exercises they will perform.
4. *Functional ability*, measured by the 2-minute-step-test (2-MST) [41], peak expiratory flow (PEF) [42], handgrip strength [43], gait speed over 15 feet [44], stair-climbing speed [45], and Timed Up&Go-Test (TUG) [46].
5. *Level of mobility and falls 12 months post-surgery*. Fall incidence will be monitored over the course of all visits. For evaluating everyday-mobility, the Life-Space Assessment will be used [47].
6. *Health-status* 12 months post-surgery
7. Psychosocial development of participants, as measured by the PHQ-8, GAD-7, and iADL-Questionnaire by Kellgren & Lawrence
8. *Healthcare resource use within 12 months post-surgery.* During follow-up, all direct medical and non-medical resource use excluding transportation and time costs will be monitored using a validated questionnaire for health-related resource use in an elderly population (Fragebogen zur Inanspruchnahme Medizinischer und nicht-medizinischer Versorgungsleistungen im Alter (FIMA)) [48, 49].
9. *Cost-effectiveness* of the prehabilitation program based on cost-utility and cost-effectiveness analyses

Study procedures

Assessments and study visits

Over the course of the study, participants will be contacted during 17 visits (V2-V18). A short description of the visits can be found in Table 2, an overview of assessment categories in Table 3.

Table 2
description of study visits

Visit	Day	Description
Phase I: Screening and inclusion in study (intervention and control group)		
V0	Day 1	Frailty-screening
V1	Day 1 / 2	Inclusion into study
V2	Day 1 / 2	Baseline assessment
Phase II: Shared Decision Making (intervention group only)		
V3	V1 /V1 + 1–5 days	SDM-conference
Phase III: Prehabilitation (intervention group only)		
V4	22–25 days before surgery	Start prehabilitation
V5	V4 + 21 days	End prehabilitation
Phase IV: Follow-Up (intervention and control group)		
V6	7–14 Days post- surgery	Discharge from hospital
V7, V8	1 / 2 months post- surgery	Telemedical / telephone interview
V9	3 months post- surgery	Follow-Up at 3 months (Telemedical / telephone interview or home visit)
V10 – V17	4–11 post- surgery	Telemedical / telephone interview
V18	12 months post-surgery	Follow-Up at 12 months (home visit)

Table 3
Trial and assessment schedule

Assessments	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	V16	V17
Frailty status	X																	
Inclusion / exclusion criteria	X																	
Informed consent	X																	
Sociodemographic data		X																
Weight, BMI		X			X			X										X
Medical data		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Care dependency		X				X			X									X
Functional Assessments		X		X	X													X
Falls		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Cognitive function		X																X
Depression		X																X
Psychosocial assessment		X							X									x
Autonomy, SDM-process			X															
Adherence to prehabilitation					X													
Medical record data			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Assessments

The various assessments to be applied in the different visits are depicted in the Spirit Figure (Additional File 4) and translated study protocol (Additional File 5).

Sociodemographic data consist of age, sex, height, weight, BMI, and level of education. Medical data includes main and secondary diagnoses, medication, and laboratory values. Medication will be assessed at baseline and during hospital stay as well as during all follow-up-visits. Polypharmacy will be identified based on the number of active pharmaceutical agents. This definition is, according to a recent systematic review, the most common definition for polypharmacy [50]. For identifying relevant co-morbidities and their potential impact on surgery outcome, the Charlson Comorbidity Index (CCI) will be applied [51]. Difficulties with hearing and seeing with and without assistive devices will be assessed with a short questionnaire.

Care dependency will be assessed with the help of two instruments. The first assessment is the aforementioned NBA [39]. Additionally, we assess care independence with the Barthel Index (BI) [52].

Functional assessments include the 2-MST [41], PEF [42], TUG [46], and stair-climbing speed [53, 54]. Additionally, handgrip strength [43] and gait speed over 15 feet [44] will be measured as part of the frailty assessment.

Falls will be monitored over the whole study period of each participant. At baseline, participants will be asked about any falls in the last 12 months as well as the number of falls of any faller. Additionally, the Activities Balance Confidence Scale in its short version (ABC-6) [55] will be used to measure balance confidence at visit 1, 4, 8 and 17. At each visit following baseline, participants will be asked about any falls since the last visit.

Cognitive function will be assessed by the MiniCog™ [56] as a screening tool. Additional cognitive tests consist of the Montreal Cognitive Assessment (MOCA) [57, 58] as well as the Trailmaking (TMT)-test part A and B [59].

Symptoms for Depression will be identified with the Patient Health Questionnaire depression scale (PHQ-8) [60]. As Depression in older people is often linked to anxiety and loneliness, we additionally assess the Generalized Anxiety Disorder Scale-7 (GAD-7) [61] and the UCLA 3-item

Loneliness Scale [62].

Psychosocial assessments include the instrumental activities of daily living (IADL) questionnaire by Lawton & Brody [63], the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) [64], as well as questionnaires on the social situation of the participant [65] and the EQ-5D-5L for assessing quality of life (QoL) [66].

As part of the preparation for the SDM process in the intervention group, the Autonomy-Preference-Index will be applied [67, 68]. After finishing the SDM process, satisfaction with the course of the process will be evaluated for participants and health professionals as well as significant others of the participant, if available, using a structured questionnaire [69].

Adherence to the prehabilitation program will be monitored through documentation of each session. This documentation includes the goal for each session (e.g., strength, endurance, balance/mobility), intensity and repetitions (strength) or duration (endurance). The Borg-Scale will be used to monitor subjective exhaustion during exercises [70]. For documenting unsupervised exercises, a patient diary will be filled out by the patient using the same information. The supervising therapists will control completeness of the diary during the supervised prehabilitation sessions.

Medical record data includes peri- and post-surgery data from the hospital record, including surgery and anaesthesia duration, anaesthesia method used, peri- and post-surgery complications, post-surgery therapy, ICU and hospital length of stay, rehabilitation duration and setting as well as post-rehabilitation therapies. Additionally, resource use, such as contacts with medical doctors and other health professions or planned and unplanned hospital stays, will be documented using the FIMA questionnaire [48]. Lastly, emergency room visits (via documentation of participating hospitals, insurance company data, or discharge letters provided by the participants), and mortality will be documented.

Randomization

After completing the baseline visit, all participants will be randomized according to a pre-defined protocol. A computer based and independently created randomized group allocation procedure will be provided and implemented by the independent statistician of the project. The randomization is internet based and will be performed with the web-based randomization tool provided by the Research Electronic Data Capture Software (REDCap) [71]. After being randomized by designated study personnel, the patient, the study centre as well as the trial management will be informed about the respective allocation.

Blinding

Due to the nature of the intervention, all participants, and all staff members in the prehabilitation centres cannot be blinded. Consequently, blinding to group allocation will be enforced for all assessors. The project coordinator, data manager and the intervention coordinator will have access to group assignment but will not be involved in assessing participants in the follow-up-phase (baseline visit assessments will be conducted before randomization).

Data collection and follow-up

Documentation

Data from all visits except for V4 and 5 as well as the documentation of the prehabilitation will be recorded directly into Research Electronic Data Capture Software (REDCap). Access to the database is controlled by password and is granted through the management committee.

The data structure for our project has been prepared to ensue comprehensive and consistent data entry. All items are controlled for the respective range and adequacy. Whenever possible, radio buttons instead of free data entry are used. Thresholds were needed (e.g. for frailty screening and data that will be included in the SDM process) are calculated automatically to minimize errors.

Data quality will be ensured by a) regular validation of the data, including checks for comprehensibility, by the study team and b) by re-education visits for all recruitment and prehabilitation centres, if necessary.

Personal information of participants will be collected after given consent to participate. These personal data will include Name, residency, and contact data of all participants. Additional information includes contact data of relatives or significant others, primary care physician, and care institutions. These data will be recorded in REDCAP, however, due to data safety reasons of the identifying information in a separate database with a three-factor authentication.

All therapy sessions within the prehabilitation will be documented either paper-based or directly in REDCap. Documentation for each session include goal of the session, performed exercises, duration of the session, intensity, number of sets and equipment used including weights, if applicable. Additionally, prescription of unsupervised exercises will be documented. The therapist running each session will provide the documentation.

After completing the study, all gathered data will be stored within the secured data storage system of the leading study centre (Charité – Universitätsmedizin Berlin).

Patient diary

For documenting all unsupervised exercises, each patient will keep a prehabilitation diary that includes the same information than the documentation form used by the therapists. Completion of the diary will be supervised by the therapist working with the patient.

Follow up visits

All participants will be followed up monthly for 12 months after surgery (see Table 2). Telephone interviews (visits 7, 8 and 10 to 17) will cover any falls that occurred in the previous month, the current medication, current pain, and the use of medical, nursing or therapeutic services. In addition, visit 9, 12 and 15 will include quality of life (EQ-5D-5L), disability (WHODAS 2.0) and questions regarding the use of health care resources.

Three months after surgery the telephone interview (see Table 2) can be facultatively extended to a home or study centre visit. In case of a home / study centre visit the same assessment as in the final follow up (V18) will be performed. Otherwise, a shortened test battery will be used that excludes all assessments that are not feasible to perform via telephone, such as functional performance tests.

Visit 18 takes place as a home visit (or alternatively at the study centre) for all included study participants. During this visit, a final assessment of the nursing care dependency level is carried out by means of the NBA. In addition, all assessments initially recorded in visits 0 and 2 are repeated to identify different trajectories within the two study groups.

Sample size and power considerations

Based on the current literature we assume the probability of change in care level in the intervention and control group as shown in Table 4 [72].

Table 4
Quantification of the intervention effect according to Müller-Mai et al., 2015

Change in care level	Intervention group	Control group
Improvement of ≥ 1 level	5%	2.5%
No change	47.5%	42.5%
Reduction of 1 level	45%	50%
Reduction of ≥ 2 levels	2.5%	5%
Sum	100%	100%

Formally, the probability of occurrence of the care levels is an ordered categorical outcome. Based on these considerations, the sample size was calculated according to Kolassa [73] with the help of nQueryAdvisor V7 (MTT2-tmpB3E4 modules; Statsols, Cork, Ireland). Based on this calculation, a sample size of 470 patients in each group will have 80% power to detect the quantified effects as shown in Table 4 above using a Wilcoxon-Mann-Whitney rank sum test with a 0.05 two-sided level. Considering 2.5% incorrect treatment allocation and 30% loss to follow-up up after 12-months, the total sample size to be allocated to the trial is n = 1378.

The recruitment plan for achieving 1378 participants within the schedule of the study assumes that every study centre should be able to recruit 10 participants per month. Therefore, we included eleven additional study centres in order to achieve our recruitment goal of 1378 participants within a recruitment period of 12 months.

Retention of the included participants will be achieved through the monthly telephone interviews, that, besides gathering the described information, serve as a way to “stay in touch” with all participants.

Discontinuing or modifying allocated intervention (prehabilitation)

All deviations from the intervention protocol will be documented. Possible deviations include but are not limited to: discontinuation because of medical reasons, inadequate adherence of the patient, or dropout of the study; shortened or prolonged intervention period because of organisational reasons; deviations from the intervention protocol, including duration, deviation or change of the defined goals; and change of setting.

Documentation and Reporting of Adverse and Serious Adverse Events

Since adverse events are to be expected in our study population, non-serious adverse events (AE) (defined as any non-critical and “untoward medical occurrence in a patient or clinical investigation subject administered an investigational intervention”) do not necessarily have a causal relationship with the intervention (adapted from the Note for Guidance on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95 July 2000). Therefore, AEs will be documented as part of the study CRF if an event is considered to be of concern or related to the study or the intervention according to the judgement of an investigator. Adverse events will be collected from enrollment in the trial until 48h after the final assessment. The patient will be followed until the event is resolved or explained (max. until day 365 after elective surgery). Frequency of follow-up is left to the discretion of the investigator.

Serious Adverse Events (SAE) are defined as unexpected and fatal or life-threatening events that are potentially related to the study intervention. The Principal Investigator must report the event in the eCRF within 72 hours of knowledge of occurrence of the event. Serious adverse events will be reported up to 48 hours after the last study visit including the following:

- If they occur during prehabilitation: Falling to the floor, cardiac arrest, unscheduled hospitalization, unscheduled intervention (e.g., cardiac catheter) or unscheduled surgery.
- If they occur during study visits in the hospital or at home (from start of visit up to 48h after the visit): Falling to the floor.

For all participants, insurance is provided for any adverse event related to study visits as well as the intervention (including traveling to and from the study / prehabilitation site).

Statistical analysis plan

Before data analyses starts, plausibility checks will be carried out.

Descriptive analyses of all included patients will be carried out after the baseline visit has been completed. Analyses will be carried out for the total sample and stratified by age, gender, intervention and control group, and frailty status. This is intended to provide a first impression of the distribution within the strata regarding all relevant outcomes. Mean and standard deviation are shown for continuous variables as well as relative and absolute frequencies for categorical variables.

The primary efficacy endpoint is the change in care level – defined as the difference between the level of care dependency at baseline and 12 months post-surgery (ΔNBA-Score = NBA-Score (V18) - NBA-Score (V2).

The prehabilitation effect is defined and tested by a non-parametric approach using the Mann-Whitney-Wilcoxon rank sum test with ties. Moreover, sensitivity analyses will be performed using multivariable logistic regression analysis to adjust for relevant confounders at baseline (e.g. age or gender) as well as to consider longitudinal data and its correlation structure [74].

Secondary endpoints, namely functional parameters, falls, cognitive functions, psychosocial factors, and health related quality of life, which will be assessed at different time points (see Table 3 visit 1 to 18), are compared between intervention and control group. Moreover, generalised linear mixed-effect regression models with changes over one year as the dependent variable will be used.

The analyses of the primary and secondary outcomes will allow for an additional adjustment for individual-specific confounding given the baseline variables such as age, gender, or frailty status.

Moreover, sensitivity analyses will be conducted to address the impact of missingness mechanism, e.g., missing at random or not at random. Complete case analyses will be compared with multiple imputation analyses. Missing data prior to the follow-up measurement will occur, because of death or for other reasons (e.g., morbidity, loss to follow-up or consent withdrawn). As it is assumed that death is a likely cause of missingness, it will be classified as the worst possible endpoint in care level.

The principal analyses will be performed according to the intention to treat principle, and not adjusted for screening or baseline covariates or site. The significance level is set to alpha = 5% (two-side). The p-value as a measure of the strength indicates the association between the dependent and the independent variables. The null hypothesis will be rejected if the p-value related to the test statistic for the treatment effect is equal to or smaller than the significance level alpha = 0.05.

The full statistical analysis plan will be finalized and published on the project website after completion of the follow-up assessments, but before starting the analyses.

Interim analyses

There will be no interim analyses.

Health economic evaluation

A protocol detailing the methods of our health economic evaluation will be published separately. In brief, we will evaluate the intervention's cost-effectiveness from the perspective of the Statutory Health Insurance (payer perspective) and its cost-utility from a societal perspective. Data on resource use will be collected using both a bottom-up approach (e.g., patient questionnaires, therapists' documentation) and a top-down approach (administrative data). We will calculate the costs of prehabilitation (intervention group only) using a micro-costing approach, and the costs of healthcare resource use within 12 months post-surgery (both groups) using standard unit costs for the FIMA questionnaire [75]. Costs will be expressed in EURO. As the time horizon is just over a year, no discounting will be applied. Different measures of effectiveness will be considered (see primary and secondary outcomes[57] in addition to quality-adjusted life years (QALYs) using survival data and the patients' QoL measured (EQ-5D-5L) and appropriate utility weights. Probabilistic and deterministic sensitivity analyses will be performed to explore any uncertainty in the results. A cost-effectiveness acceptability curve will be drawn to determine if prehabilitation is cost-effective under different assumptions for willingness to pay.

Management Committee and Data Safety Monitoring Committee

We established both a Management Committee (MC) and a Data Safety Monitoring Committee (DSMC) to ensure a straightforward and safe study process.

The MC is responsible for developing the study protocol, training of all assessors and health professionals involved in the intervention as well as for the initiation of new study centres. Additionally, the MC will monitor all study procedures in all study centres and will ensure adherence to measurement and intervention protocols as well as ethical guidelines. Deviations from any protocol will be documented and reported.

An independent Data and Safety Monitoring Committee (DSMC), consisting of experts in clinical studies, biostatistics and perioperative, and rehabilitation medicine, has been established to monitor recruitment, protocol adherence, as well as monitoring follow-up and safety data. Virtual meetings and face-to-face meetings will be conducted. The MC as well as the DSMC may independently request video conferences. The results of all meetings are protocolled. Accumulated trial data will be reported to the DSMC by the study statistician. The DSMC will assess the trial progress and safety. As a primary responsibility, the DSMC will consider and assess treatment safety (e.g., serious adverse events (SAEs) or deaths). Based on these deliberations, recommendations will be made by the DSMC when appropriate to the PRAEP-GO MC about stopping or continuing the trial. At their discretion the DSMC may also formulate recommendations relating to the selection/recruitment of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The MC will be responsible for promptly assessing any DSMC correspondence or recommendations, to decide whether to continue or terminate the trial, or suspend enrolment and to determine whether amendments to the protocol or changes in study conduct are required.

Dissemination plans

The study report will be submitted for publication to a peer-reviewed medical journal. In addition, it will be made available via the department's website. Furthermore, a study report will be submitted to the Federal Joint Committee (G-BA).

A summary report of the finals study results will be disseminated to all project partners and on the project homepage. All authorship in all scientific publications will adhere to the recommendations of the International Committee of medical journal editors [76].

Discussion

PRÄP-GO is the first trial to investigate the effect of a shared decision-making conference and 3-week prehabilitation program in a general surgical, (pre-)frail population. Up to now, evidence exists for a variety of specific surgical procedures [27]. Prehabilitation is according to Wynter-Blyth and Moorthy "a strategy to begin the rehabilitation process before surgery […]" [77]. Le Roy et al. emphasized the multimodal nature of prehabilitation and recommended to include a) physical exercise training, b) nutritional care, and c) psychological support as part of the multimodal intervention during prehabilitation [78]. While these definitions offer a general idea on the concept and goals of prehabilitation, a broader and more specific framework on how to organize and execute such a program is mostly lacking. One of the reasons for this is that most trials on the effectiveness of prehabilitation evaluate specific patient groups and/or surgical procedures.

Hughes et al. performed a systematic review and meta-analysis on prehabilitation programs before major abdominal surgery. They included 15 RCTs with 907 participants that reported on a variety of abdominal surgical procedures. In this review, prehabilitation lead to a significant reduction in morbidity, but not in LOS or functional recovery [79]. In contrast, Gillis et al. reported a significant reduction in length of hospital stay in a systematic review on prehabilitation, consisting of a nutritional intervention with and without additional exercises before colorectal resection surgery. The three out of nine RCTs which reported on functional outcomes, also reported a significant improvement [20]. In 2017,

another systematic review on prehabilitation before abdominal cancer surgery with nine studies and a total of 549 participants on different surgical procedures was published. There were heterogeneous results on functional walking capacity, cardiopulmonary fitness, anxiety, post-operative complications, and health-related quality of life, as well as a high variety of the performed programs, with prehabilitation duration ranging between 2 and 8 weeks as well as a vast variety of therapeutic concepts that included one to three therapeutic modes (diet counselling, physical exercise, and psycho-social support) [80]. Of note, the physical exercise intervention consisted of walking and/or endurance exercises in all included studies. In another meta-analysis, nine studies with 435 participants receiving intra-abdominal surgery for cancer- and non-cancer-related medical reasons were analysed. The authors found a significant reduction in morbidity (OR 0.59 [0.38, 0.91] vs. control; OR 0.35 [0.17, 0.71] vs. usual care) and a significant reduction in postoperative pulmonary complications (OR 0.27 [0.13, 0.57] vs. control), but no significant reduction in LOS [81].

For orthopaedic surgical procedures, Gometz et al. (2018) performed a systematic review for prehabilitation before spinal surgery. They included 5 RCTs on 3 different projects that included 217 participants. While none of the included RCTs reported any significant differences in pain or disability after surgery, 2 of these studies reported a significant reduction of total costs in the prehabilitation groups [82]. Wallis et al. reported on a systematic review and meta-analysis on pre-operative intervention before knee or hip joint replacement surgery that included 23 RCTs with 1467 participants. The results of this review suggested that, based on the included studies, prehabilitation can significantly reduce pre-operative pain and, when including educational intervention, is able to improve post-operative activity [83]. In another systematic review on prehabilitation before knee or hip arthroplasty surgery, Vasta et alincluded 14 studies with 1175 participants. Although they found inconsistent evidence, most included studies reported postoperative improvements in pain, range of movement, quality of life, and functional scores for knee patients while for hip patients, no robust conclusions could be drawn [84].

For prehabilitation for older persons with frailty or pre-frailty, Milder et al. included 8 studies, with 2 of them representing ongoing studies. The six published studies included 168 participants. The included studies were highly heterogeneous, although five of the six finished studies could demonstrate positive effects of the respective prehabilitation program, including improved function, reduced complication rates, and reduced mortality [85]. In another systematic review, Baimas-George et al. included five studies with 265 participants on prehabilitation in patients with frailty. Again, the included studies were heterogeneous, but could demonstrate positive effects regarding LOS; mortality, and distance during 6-Minute-Walk-Test [86].

While these reviews demonstrate that a multitude of publications on prehabilitation in different settings exist, there is still a lack of robust evidence regarding its (cost-)effectiveness in a general surgical, (pre-)frail population.

A novel approach pursued in our trial is to include SDM into the concept of prehabilitation. As part of a European project on identifying factors for a successful implementation of principles of integrated care, a mixed-methods study on involvement preferences of geriatric patients was conducted [32]. While the results suggested that older people in acute need of care had a significantly lower preference to be involved in a SDM process, results from qualitative interviews showed that a lack of a proper information and education process was at least in part responsible for the lack of willingness to be involved in the care process. We therefore establish a SDM process based on a framework and recommendations for setting up a SDM process for frail older people [87]. To our knowledge, the inclusion of a SDM process into a concept of prehabilitation has not been implemented so far.

In contrast to most other studies in the field of prehabilitation, we deliberately chose not to limit our group of potential participants to a single surgical intervention or indication. Therefore, our medical exclusion criteria regarding surgical interventions were limited to non-delayable and intracranial procedures. Additionally, our primary endpoint as well as many of our secondary endpoints reflect general factors contributing to health, QoL, and self-dependence. As such, these factors are expected to play a role in any evaluation of patient-centred interventions regardless of the type of intervention.

In addition, our approach will result in a cohort that reflects the diversity of routine clinical practice. Being funded by the innovation fund of the Federal Joint Committee, the highest decision-making body of the joint self-government of physicians, dentists, hospitals and health insurance funds in Germany, the intervention concept is being evaluated to determine whether it should be accepted into the routine care of the statutory health insurance funds in Germany.

Choice Of Endpoints

Statutory health insurance in Germany generally covers the costs of medical treatments and care assistance [88]. In the latter case, the need for care assistance is evaluated using the NBA by a specialised nurse or medical doctor before care assistance payments can start [38]. In Germany, costs for care needs are covered based on the solidarity principle, i.e., the payments of the insurants are used to cover costs of the care provided to those in need [88]. Therefore, statutory health insurance companies in Germany have a special interest and obligation to avoid costs due to circumstances that can be avoided by provident measures [89]. For this reason, the primary endpoint is of particular interest for

the German health care system since the NBA was designed not only to evaluate whether a given person needs nursing care, but also if the costs of this care will be reimbursed by the insurance. Therefore, the NBA measures care need based on reported difficulties in performing activities of daily living. While a validation study to evaluate time and effort of care based on the different care levels do exist [90], further validation studies regarding reliability and the existence of floor / ceiling effects, among others, are lacking.

Nevertheless, we decided to use the NBA as our primary endpoint because it enables us to use it for an effectiveness analysis from the patients' perspective and about the impact our prehabilitation programme can have from a health economic perspective. To compensate for the existing shortcomings of the NBA, we analyse several secondary outcomes including functional, cognitive, and psychosocial parameters as well as outcomes related to medical care such as peri- and post-surgery complications, LOS and post-discharge utilization of the health care system.

Limitations

While the protocol we are presenting here encompasses many strengths, some limitations remain. We identified three sources of potential bias in our study that need to be discussed.

First, as in all RCTs on therapeutic interventions, a proper blinding of participants and health professionals taking out the intervention is not realistic to achieve. We are limited to perform outcome-assessor blinding and a blinded statistical analysis.

Second, therapeutic intervention studies lack standardisation of the intervention, at least if one defines "standardisation" as a rigorous effort to provide the same treatment to all participants. Since a fully standardised intervention is usually not useful in therapeutic trials, it is important to provide sufficient information about the treatment framework and how the intervention is planned and adapted to the needs of the participants. Unfortunately, many therapy studies still lack a proper description of their respective intervention [91–93]. In PRAEP-GO a proper description of the therapy is provided by a) describing the process for the arrangement of our intervention in detail and b) ensuring that the performed therapies are appropriate to attain the goals for each patient, which were defined in a standardized process themselves. Additionally, all exercise regimes were based on evidence-based recommendations like the American College of Sports Medicine for exercise and physical activity in older adults [94, 95].

The third limitation concerns our study population. Frail elderly as a group are still very heterogeneous from a medical perspective. This may affect the effectiveness in the study. However, a positive evaluation of the study can be assumed to have a high general validity.

Trial Status

The first patient was randomized on 30 Jun 2020. The trial was paused from 1st of November 2020 till March 1st 2021 due to the COVID-19 pandemic. Recruitment will continue until the complete sample size is achieved, which is expected to be in June 2022.

Abbreviations

2-MST	2-minute-step-test
ABC	Activities Balance Confidence Scale
ADL	Activities of Daily Living
CCI	Charlson Comorbidity Index
DSMC	Data Safety Monitoring Committee
FIMA	Fragebogen zur Inanspruchnahme Medizinischer und nicht-medizinischer Versorgungsleistungen im Alter [engl.]
GAD-7	Generalized Anxiety Disorder Scale
G-BA	„Gemeinsamer Bundesausschuss“ [engl. Federal Joint Committee]
GOLD	Global Initiative for Chronic Obstructive Lung Disease
iADL	instrumental Activities of Daily Living
ICU	Intensive Care Unit

LOS	Length of Stay
MC	Management Committee
MET	Metabolic Equivalent of Task
MOCA	Montreal Cognitive Assessment
NBA	“Neues Begutachtungsassessment”
NYHA	New York Heart Association
RCT	randomised, controlled trial
SAE	Serious Adverse Event
SDM	Shared Decision-Making
OEP	Otago Exercise Program
OR	Odds Ratio
PEF	Peak Expiratory Flow
PHQ-8	Patient Health Questionnaire depression scale
QALY	Quality Adjusted Life Years
QoL	Quality of Life
TUG	Timed Up&Go-Test
UCLA	University of California, Los Angeles
WHODAS	WHO Disability Assessment Schedule

Declarations

Acknowledgements

Members of the PRÄP-GO consortium are: Charité – Universitätsmedizin Berlin (executing entity: Department of Anesthesiology and Operative Intensive Care Medicine (CVK/CCM), Prof. Dr. med. Claudia Spies), BARMER health insurance (executing entity: Intitute for health system research, Dr. med. Ursula Marschall), St. Joseph Krankenhaus Berlin-Tempelhof GmbH (executing entity: Clinic for Geriatrics, Dr. med. Rahel Eckardt-Felmberg; Hausarztpraxis Landgraf (Dr. med Irmgard Landgraf), Brandenburg Medical School Theodor Fontane (executing entity: Institute of General medicine, Prof. Dr. med. Ulrich Schwantes), Technische Universität Berlin (executing entity: Department of Healthcare Management, Prof. Dr. med. Reinhard Busse), Ludwig-Maximilians-Universität München (executing entity: Institute for Medical Information Processing, Biometry, and Epidemiology, Prof. Dr. rer. nat. Ulrich Mansmann).

The PRÄP-GO investigators can be found in Additional File 1.

SPIRIT guidelines

The PRÄPGO trial study protocol was written in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [16]. The SPIRIT checklist is included in Additional File 2. The SPIRIT figure is Additional File 4.

Authors’ contributions

The PRÄP-GO consortium members applied for funding of the project and built the legal representation of the project. CS is the principal investigator; she conceived the study, led the proposal and protocol development. SJS is her deputy, he contributed to the study design and protocol development. KS is the study coordinator; she contributed to the study design and protocol development. UM is the independent study

statistician, he contributed to the study proposal and protocol development. RB, WQ and TR are responsible for the health economic evaluation. CS, SJS, KS, RM and JK represent the management committee of PRÄPGO and were involved in the protocol development and in ethical approval. VL supervises the randomization, is involved in the data management (quality checks) and contributes to the project management.

SJS and JK drafted the manuscript. All authors critically revised the manuscript and approved its final version.

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The G-BA had no role in study design; collection, management, analysis, and interpretation of data, writing of the report; and the decision to submit the report for publication.

Availability of data and materials

The Institute for Medical Information Processing, Biometray, and Epidemiology of the Ludwig-Maximilian University Munich will handle the randomization as well as the data analysis. The health care economic evaluation will be performed by the Department of Healthcare Management of the Technische Universität Berlin. The study database, monitoring, and safety reporting are operated by the Department of Anesthesiology and Operative Intensive Care of the Charité – Universitätsmedizin Berlin. Regularly safety reports are generated and distributed to the Data Safety and Monitoring Committee. De-identified datasets can be made available on reasonable scientific request to the management committee after the primary publication. Access might be restricted due to German data protection laws.

Ethical approval and consent to participate

The study has been approved by the ethical committee of the Charité – Universitätsmedizin Berlin as the primary study centre (approval number EA1/225/19, see Additional File 7). Any participation study centre will either join the ethical approval of the Charité or, if needed, will have the study approved by the respective responsible ethical committee before starting to include patients. The study is registered at ClinicalTrials.gov with the trial registry number NCT04418271 and has the Universal Trial Number (UTN) U1111-1253-4820. The current study protocol is version 1.1 (13.06.2020). The trial will be conducted in agreement with the principles of the Declaration of Helsinki. All participants will be informed about the purpose of the trial, the risks, and the potential benefits. There is no anticipated harm and compensation for trial participation. Written informed consent will be obtained by the local study physician from each participant. The Department of Anesthesiology and Operative Intensive Care Medicine of the Charité – Universitätsmedizin Berlin coordinates the study. The original study protocol (in German) and the statistical analysis plan including amendments are publicly available at www.praep-go.de.

Protocol amendments

Any changes to the protocol that affect or could affect the study design or procedures, the objectives and hypotheses, or patient safety must be submitted as an amendment to the ethics committees of the study centres for consultation. The new version of the study protocol will be made available at the project’s website, including the rationale for any changes. The Clinical Trials entry will be adjusted if necessary.

Minor changes, such as organisational adjustments, changes in written manuals for the pure reason of clarification of any processes, or changes in responsibilities that have no effects on the defined study goals and conduction, will be agreed upon by the management committee of PRAEP-GO. In such cases, the ethical committee of the leading study centre will be notified of such changes.

Consent for publication

Not applicable.

Competing interests

SJ Schaller reports personal fees for educational purposes from Springer Verlag GmbH (Vienna, Austria) and for lectures from Fresenius (Bad Homburg, Germany), grants and non-financial support from ESICM (Brussels, Belgium), Fresenius (Bad Homburg, Germany), STIMIT AG (Biel, Switzerland), and Reactive Robotics GmbH (Munich, Germany) as well as from national (e.g. DGAI) and international (e.g. ESICM) medical societies (or their congress organizers) in the field of anesthesiology and intensive care, all outside the submitted work; SJS holds stocks in small amounts from Alphabeth Inc., Bayer AG, Rhön-Klinikum AG, and Siemens AG. These did not have any influence on this study.

J Kiselev reports no competing interests.

V Loidl reports no competing interests.

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R Mörgeli reports no competing interests.

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Figures

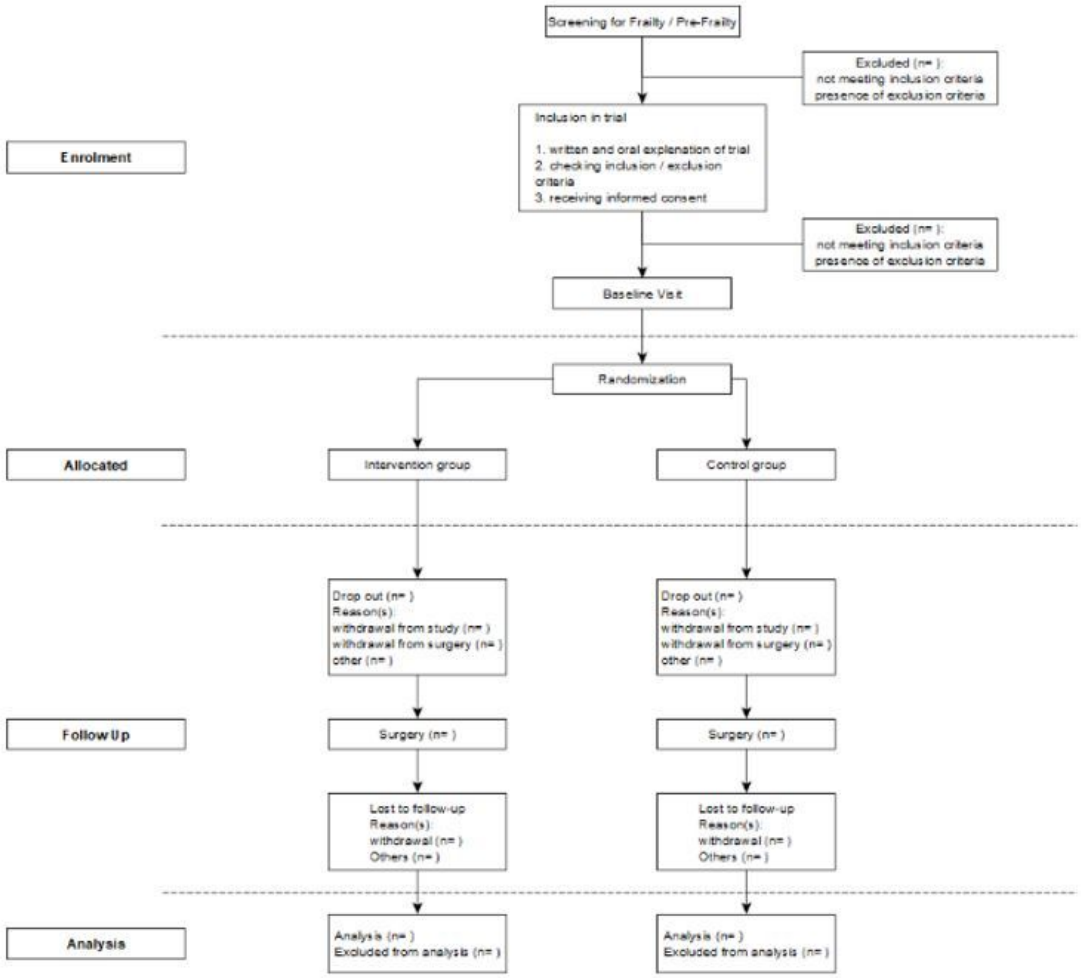

Figure 1

flowchart of the trial

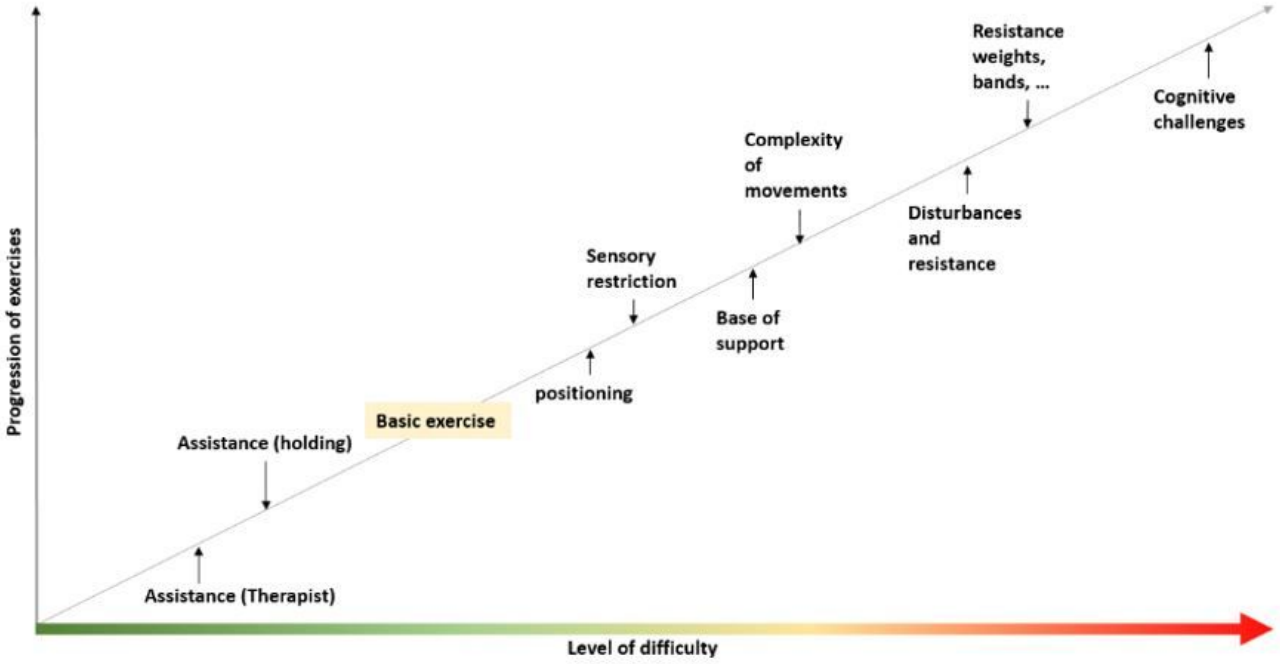

Figure 2

exercise progression in prehabilitation (adapted from: [38]

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