TEMPLATE RESEARCH PROTOCOL

(November 2024)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018
- April 2024: link to template protocol to be used for CTR studies added and additional explanation and comments in section 9 Safety reporting
- Nov 2024: removal of information related to studies with a medicinal product and replacing ToetsingOnline with Research Portal that will be launched on February 3, 2025.

PROTOCOL TITLE: PlAnt Vs animal based Oral nutritional Supplements: Patients' opinions and Nutritional outcomes: A multicenter pilot feasibility study (PAVOS)

Protocol ID	
Short title	Plant-based vs animal-based oral nutritional supplements
Version	4.0
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Laboratory sites	Not applicable
Pharmacy	Not applicable

PROTOCOL SIGNATURE SHEET

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	**Adverse Event**
BIA	**Bioelectrical Impedance Analysis**
BMI	**Body Mass Index**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
DSMB	**Data Safety Monitoring Board**
EPR	**Electronic Patient Record**
ESPEN	**European Society of Parenteral and Enteral Nutrition**
FM	**Fat Mass**
FFM	**Fat-Free Mass**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
MNA	**Mini Nutritional Assessment**
MUST	**Malnutrition Universal Screening Tool**
ONS	**Oral Nutritional Supplements**
PG-SGA-(SF)	**Patient Generated Subjective Global Assessment (Short Form)**
Review Committee	**Medical research ethics committee (MREC) or CCMO**
RCT	**Randomized Controlled Trial**
RNIT	**Randomized Controlled Non-Inferiority Trial**
(S)AE	**(Serious) Adverse Event**
SNAQ	**Short Nutritional Assessment Questionnaire**
SPPB	**Short Physical Performance Battery**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SQUASH	**Short Questionnaire to Assess Health-enhancing physical activity**
TUG	**Timed Up and Go**

UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WHO	**World Health Organization**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Risk of malnutrition is a common condition in hospitalized patients, with a prevalence up to almost 40% depending on the specific patient population. As part of the dietary counseling, oral nutritional supplements (ONS) (i.e., energy and protein-rich drinks) are advised when habitual oral nutritional intake remains inadequate (75% of protein and energy requirements). ONS are effective in increasing total energy and protein intake, resulting in less complications and re-admissions, as well as improved body weight and physical functioning.

Recently the Dutch Ministry of Health, Welfare and Sport and the Dutch Federation of University centers signed the Green Deal “Working together on sustainable care” in which they agreed on “Green and climate neutral care” by 2026. This also includes meeting criteria for purchasing medical and non-medical nutrition in hospitals for future tenders.

The development of ONS transitioning towards more plant-based proteins already receives much attention, which is deemed relevant in terms of overall sustainability. However, so far no studies have investigated the effectiveness of long-term use of plant-based ONS on an adequacy of protein and energy intake, nutritional status, muscle status, as well as physical and clinical outcomes. Hence, further research is needed to address the knowledge gaps on effectiveness of plant-based ONS. Yet, before conducting a randomized controlled trial (RCT), it is essential to first assess the feasibility of such a study in terms of patient recruitment, drop-out rates, adherence, and feasibility of study measurements. The current protocol describes this pilot feasibility, the results of which will provide essential insights to subsequently setup a study protocol for a full scale RCT to address effectiveness of plant-based ONS vs (traditional) animal-based ONS. Thus, this pilot feasibility study aims to assess the feasibility of a multicenter randomized controlled non-inferiority trial (RNIT) to compare plant-based ONS versus animal-based ONS.

Objective: The primary objective of this study is to investigate the feasibility (patient recruitment, drop-out rate, adherence, and study measurements) of a multicenter RNIT comparing plant-based versus animal-based ONS. The secondary objective of this study is to evaluate the energy and protein intake versus requirements, nutritional status, muscle status, physical and clinical outcomes, and patient's satisfaction with long-term supplementation.

Study design: A multicenter pilot randomized feasibility study

Study population: Patients from the medical oncology, lung diseases, cardiology, cardiothoracic surgery, and orthopaedic departments at risk for inadequate nutritional intake treated at Maastricht UMC+ and Radboudumc.

Intervention (if applicable): the intervention group receives plant-based ONS (Fresubin® Plant-based Drink vanilla) and the control group receives animal based ONS (Fresubin® Yodrink raspberry) during hospital admission/treatment and up to 3 months after.
Main study parameters/endpoints: The primary endpoint of the study is the feasibility of the RNIT with respect to the recruitment, drop-out, adherence, and study measurements.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: This study will not cause much additional burden on the patients in addition to their normal treatment as measurements are carried out during their hospital admission, or when possible, they are already present in the hospital for another appointment at the outpatient clinic. There will be two moments where measurements will be performed. The additional time needed to performing the measurements of this study will be approximately 90 minutes, both at the start and at the end of the intervention period. After one and after two months, a short ‘check-in’ will be done (phone call or at the hospital if patient has appointment there), this takes approximately 10 minutes.
The participants are asked to perform 3 physical tests and complete questionnaires, which could be experienced as exhausting/ a burden. There are no further risks associated with this research. Patients will not perceive direct benefits from participation in this study. It is expected that the use of ONS will increase energy and protein intake of the participants, which in turn could improve their nutritional status.

1. INTRODUCTION AND RATIONALE

Risk of malnutrition is highly prevalent in hospitals, with prevalence rates up to almost 40% on hospital admission, depending on the specific patient population (1-3). Especially in oncological, surgical and elderly patients, malnutrition is very common with reported prevalence ranging from 21% of severe risk on malnutrition up to even 40% in specific cancer types such as head and neck, gastrointestinal, lung, ovarian and urological cancer (4,5) and up to 66% in older patients in acute care and rehabilitation (6). Malnutrition is associated with poor physical functioning, impaired wound healing, complications, prolonged duration of hospitalization, lower quality of life and increased mortality (7-9). In the Netherlands, the additional health care costs associated with malnutrition are estimated at an annual € 1.8 billion (10). Given its prevalence and the associated negative health consequences, the Dutch Inspectorate of Health and Youth has included 'Malnutrition' in the "Basic set of medical specialist care" as a target for improvement for 2023 and beyond. The objective for improvement described in this Basic set is to diagnose and treat malnutrition in an early phase before, during and/or after hospitalization, while also giving special attention to continuation of treatment after discharge, in the home situation (11). In all Dutch hospitals, patients should be screened for malnutrition upon hospitalization (MUST ≥2/SNAQ≥3/PG-SGA-SF ≥9).

Throughout hospitalization, food intake of patients is often inadequate, due to reduced appetite and disease impact symptoms, such as pain, nausea, decreased taste and smell (12). Adding further complexity to this problem, nutritional requirements are increased due to illness, treatment and the healing process. As such, it can be challenging to adequately meet the nutritional requirements during the course of hospitalization and rehabilitation. Patients at risk of malnutrition will receive individual counseling by a dietitian, aimed at reaching adequate protein and energy intake. As part of this nutritional counseling, oral nutritional supplements (ONS) (i.e., energy and protein-rich drinks) are advised when habitual oral nutrition remains inadequate (75% of protein and energy requirements) (13). ONS are effective in increasing total energy and protein intake, resulting in less complications and re-admissions, as well as improved body weight and physical functioning (14). Currently available ONS mostly contain animal-based proteins, usually in the form of dairy proteins, ensuring high-quality proteins with regard to digestibility, amino acid composition, and bioavailability.

Recently the Dutch Ministry of Health, Welfare and Sport and the Dutch Federation of University centers signed the Green Deal "Working together on sustainable care" in which they agreed on "Green and climate neutral care" by 2026. One of the five goals is to stimulate "a healthy, varied, more plant-based and sustainable diet" (15). This also includes

meeting criteria for purchasing medical and non-medical nutrition in hospitals for future tenders.

Already much attention is given to replacing part of the animal-based protein in hospital diets with plant-based protein sources, which is deemed relevant in terms of overall sustainability as well as enabling to feed the ever-growing world's population (16). Although in general, plant-based proteins are assumed to be of less nutritional value (e.g., less complete amino acid profile, lower digestibility), more and more options are being developed to improve the bioavailability and nutritional value of more sustainable, plant-based proteins, thereby supporting their use to meet specific protein and amino acid requirements. For example, various legumes such as soy, lentils, and pea, and/or (combinations of) wheats and nuts, and even insect proteins have been suggested as alternative protein sources. The first studies in young, healthy adults even confirm that ingestion of an ample amount of (combinations of) such plant-based proteins can induce a similar anabolic response as compared to high-quality milk protein (17). One of the important factors that drives the anabolic response to protein ingestion is the essential amino acid content of the protein with leucine being of particular importance (18). In this respect, soy protein is traditionally viewed as a relevant plant-based protein source due to its excellent digestibility as well as its relatively high essential amino acid content (27%) and leucine content (19). Although soy protein supplementation has been suggested as a promising strategy for maintaining muscle mass and function in older people, the more long-term effects in both healthy and more compromised (clinical) populations remain to be established (20).

The transition towards more plant-based ONS already receives much attention. However, it is unknown whether patient satisfaction (e.g., taste, smell, satiety, opinion) of plant-based ONS is similar compared to regular animal-based products. Moreover, so far the effectiveness of plant-based ONS to support adequate protein and energy intake, nutritional status, muscle status, as well as physical and clinical outcomes with long-term supplementation has not been investigated. Hence, further research is needed to address these knowledge gaps. However, before conducting a randomized controlled trial (RCT), it is essential to first assess the feasibility of such a study in terms of patient recruitment, drop-out rates, adherence, and feasibility of study measurements. The current protocol describes this pilot feasibility study, the results of which will be used to setup the study protocol for full scale RCT. This pilot feasibility study aims to assess the feasibility of a (subsequent) multicenter randomized controlled non-inferiority trial (RNIT) to evaluate energy and protein intake versus requirements in patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for inadequate nutritional intake when using plant-based or animal-based ONS.

2. OBJECTIVES

Primary Objective:

The primary objective of this study is to investigate the feasibility (patient recruitment, drop-out rates, adherence, and study measurements) of a multicenter RNIT comparing plant-based versus animal-based ONS in patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for inadequate nutritional intake.

Primary research question:

What is the feasibility of a multicenter RNIT comparing plant-based ONS versus animal-based ONS in patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for inadequate nutritional intake with respect to the patient recruitment, drop-out rates, adherence, and study measurements?

Sub-questions:

Recruitment:

- What is the recruitment rate?
- What are characteristics of included and excluded patients (per patient group)?

Drop-out:

- What is the drop-out rate (percentage of patients that dropped out)?
- At what time points in the study (week number after inclusion) do patients drop out?
- What are reasons for dropping out?

Adherence:

- What is the percentage of ONS consumed versus advised?
- What are the reasons of not filling out questionnaires?

Study measurements:

- What is the percentage of successfully performed measurements?
- What are reasons for unsuccessful measurements?

Secondary Objective(s):

To assess the energy and protein intake, nutritional status, muscle status, physical and clinical outcomes, and patient’s satisfaction of long-term use of ONS.

Secondary research questions:

1. What is the energy and protein intake in patients receiving plant-based ONS with patients receiving animal-based ONS?

2. How do nutritional status, muscle mass status, physical and clinical outcomes differ between patients using plant-based ONS compared to patients using animal-based ONS?

3. How are the plant-based ONS and animal-based ONS evaluated regarding patients' satisfaction (taste, smell, satiety), their wishes and needs, and their opinion about sustainable nutrition?

3. STUDY DESIGN

This study is a pilot randomized feasibility study in patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for inadequate nutritional intake to evaluate feasibility and patient satisfaction necessary to determine a suitable patient population and calculate the sample size for a larger RNIT (i.e. study 2). In study 2, a large RNIT will be conducted to establish the long-term efficacy of plant-based vs animal-based ONS. During this pilot study, patients who are advised ONS according to usual care and signed informed consent (IC) will be randomized to receive either plant-based ONS or animal-based ONS. Several measurements will be performed at 0 and 3 months. A total of 60 patients will be included. The main aim is to establish the feasibility in terms of recruitment, drop-out rate, adherence, and study measurements of the different subpopulations, reflecting feasibility for performing study 2. Furthermore, we will collect data on protein and energy intake, which will be used for the sample size calculation of study 2. Apart from the quantitative measurements, study 1 will also be setup as a qualitative study to determine patients' satisfaction, wishes and needs towards the ONS. Data on patients' satisfaction will only be used as observational data, no comparison between the two types of products will be made.
Measurements will be performed during hospital admission, or before/after an already scheduled appointment at the hospital outpatient clinic (baseline T0), and three months after baseline (T3). Within these 3 months, patients will be contacted by the researcher 1 month after the start (T1) and 2 months after the start (T2) for a 'check-in' conversation. For this conversation the researcher will either make a phone call or have brief conversation at the

hospital if the patient is already there for another appointment. The researcher will ask about any changes in body weight, discuss changes in the nutritional advice provided by the dietitian, ensure the patient is still correctly filling out the logbook, and address any questions or concerns related to the study. The study will be conducted at Radboud university medical center (Radboudumc) in Nijmegen, the Netherlands, and Maastricht University Medical Center (Maastricht UMC+) in Maastricht, the Netherlands.

4. STUDY POPULATION

4.1 Population (base)

The study population will consist of patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for inadequate nutritional intake treated at Radboudumc or Maastricht UMC+.

4.2 Inclusion criteria

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

- Clinical patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients age ≥18 years, and treated at Radboudumc or Maastricht UMC+.
- Patients who have been advised at least 2 bottles of ONS daily based on their nutritional requirements.
- Written informed consent (IC)

4.3 Exclusion criteria

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

- Patients who are or become dependent on tube or parenteral nutrition
- Patients where life-extending therapy is no longer possible
- Unable to follow up study instructions
- Lactose intolerance
- Soy allergy/intolerance
- Vegan diet
- Patients who have used ONS in the past six months

4.4 Sample size calculation

We aim to enrol a convenience sample of 60 patients in this feasibility study, with n=30 per study group (i.e. plant-based vs animal-based ONS) which is deemed sufficient to answer the primary research question (21, 22).

If the results of this study show that the intervention can be considered feasible, future research with a fully powered sample size shall be performed to investigate the effect of the intervention on all parameters.

5. TREATMENT OF RESEARCH PARTICIPANTS

5.1 Investigational product/treatment

Intervention product: plant-based ONS, Fresubin® Plant-based Drink vanilla. This will be compared to regular ONS, Fresubin® Yodrink raspberry with a similar nutritional content, i.e. 200ml, 300 kcal, 15 gram protein.

If the patient approves to participate in this study and signed the written IC then the patient will be randomised to one of the 2 groups: plant-based ONS or animal-based ONS.

5.2 Use of co-intervention (if applicable)

Not applicable

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

6.1.1. Plant-based

Investigational product is Fresubin® Plant-based Drink vanilla.

6.1.2. Animal-based

Control products is Fresubin® Yodrink raspberry.

Both types of ONS have the same nutritional content, i.e. 200ml, 300 kcal, 15 gram protein

6.2 Summary of findings from non-clinical and studies

Not applicable, there are no previous studies done with this plant-based ONS that is related to this research.

6.3 Summary of findings from clinical studies

Not applicable, no previous studies with this plant-based ONS have been performed before.

6.4 Summary of known and potential risks and benefits

There are no potential risks associated with this research. Patients will receive ONS as part of their regular treatment, however, with participating in this study they will be randomized to receive either the plant-based or animal-based ONS. Both types of ONS are already available and used in hospitals. Participating in this study has no specific additional benefit. Generally, the use of ONS is expected to increase the energy and protein intake for patients at risk for malnutrition, which in turn improves nutritional status.

6.5 Description and justification of route of administration and dosage

The dietitian or nurse will decide the number of bottles the patient needs per day, fully in accordance with usual care. The advice of the dietitian or nurse needs to be at least 2 bottles ONS a day for patients to be eligible to participate in this study. This is based on their nutritional intake observed by the nurse or the dietitian will base this advice on their nutritional requirement at the start of their treatment. 2 bottles of ONS is equal to 600 kcal and 30g protein. This means that there need to be a gap between their intake and requirements of ≥600 kcal and ≥30 g protein, in order to advice the ONS. Nutritional requirements will be estimated for protein intake as 1.5-1.9 g/kg fat-free mass (FFM)/d and energy intake WHO formula + surcharge up to 50% according to the Dutch guidelines of malnutrition and the ESPEN guidelines Clinical nutrition in surgery, cancer, and geriatrics (6, 13, 23, 24).

If the patient approves to participate in this study and signed the written IC then the patient will be randomised to one of the 2 groups: plant-based ONS or animal-based ONS.

6.6 Dosages, dosage modifications and method of administration

Dosage depends on advise of the dietitian or a nurse. This could be 2 bottles or more. Throughout the 3 months of the study, the advised amount of ONS may be adjusted to more or less bottles a day. This depends on their energy and protein intake and their requirements. Patients will record this advice in their logbook to ensure clarity to the researcher. The researcher will check this logbook with the patient.

7. NON-INVESTIGATIONAL PRODUCT

Not applicable

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

7.2 Summary of findings from non-clinical studies

7.3 Summary of findings from clinical studies

7.4 Summary of known and potential risks and benefits

7.5 Description and justification of route of administration and dosage

7.6 Dosages, dosage modifications and method of administration

7.7 Preparation and labelling of Non Investigational Medicinal Product

7.8 Drug accountability

8. METHODS

8.1 Study parameters/endpoints

8.1.1 Main study parameter/endpoint

The primary endpoint of the study is the feasibility (patient recruitment, drop-out rates, adherence, and study measurements) of a multicenter RNIT comparing plant-based and animal-based ONS in patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients at risk for an inadequate nutritional intake.

8.1.2 Secondary study parameters/endpoints (if applicable)

The secondary endpoints of this study is the energy and protein intake, nutritional status, muscle status, physical and clinical outcomes, and patient's satisfaction with long-term supplementation.

8.1.3 Other study parameters (if applicable)

Not applicable

8.2 Randomisation, blinding and treatment allocation

Patients will be randomized to either the plant-based ONS or animal-based ONS. Randomisation will be done by Castor EDC database. This system will generate the randomisation performed by stratification for 3 different patient populations: (1) oncology, (2) pulmonary diseases (3) other (including cardiology, cardiothoracic surgery, orthopaedic patients) and for the study location (Radboudumc and Maastricht UMC+). In this way, it will be done independently. Patients can not be blinded in this study since it is

not feasible to cover every bottle the patients drink in those 3 months (i.e. patients will receive already existing products with standard packaging and labelling). Nevertheless, the analyses will be carried out in a blinded manner.

8.3 Study procedures

Measurements during this study will be combined as best as possible during appointments planned within routine care at the hospital. Baseline measurements will take place at the start of the ONS treatment (T0) during hospital admission or during an appointment at the outpatient clinic. 1 month after the start (T1) and 2 months after the start (T2) the researcher will have a brief 'check-in' via a phone call or a conversation at the hospital if the patient is there for another appointment. 3 months after initiation (T3) the same measurements will be performed as at baseline (T0). In addition, at T3, the researcher will conduct an interview about patients' satisfaction about the ONS (Table 1).

Table 1: Overview of the study measurements for each time point.

Measurements	**Treatment initiation (T0)**	**1 month after initiation (T1)**	**2 months after initiation (T2)**	**3 months after initiation (T3)**
Body height, body weight, usual body weight, BMI	X	X	X	X
Nutritional intake (protein and energy)	X			X
Compliance ONS	X	X	X	X
Check-in conversation		X	X	
Nutritional status (PG-SGA, fat mass and fat-free mass, and muscle thickness)	X			X

Hand grip strength	X			X
Physical Activity (SQUASH)	X			X
Physical performance (TUG, SPPB)	X			X
Quality of life (EORTC-QoL-C30) and Clinical outcome measures (length of hospital stay, complications, readmission and mortality)	X			X
Patient's satisfaction about the Oral nutritional supplements				X

Body height, body weight, BMI are measured on a calibrated scale and stadiometer. Usual body weight will be asked. During the check-in process, patients are required to weigh themselves either at home or at the hospital, if they have another appointment scheduled there.

Nutritional intake and compliance of oral nutritional supplements used during hospital admittance will be measured by food registration in the Electronic Patient Record (EPR) registered by the nutritional assistant with a cross-check of a nutritional researcher. Additionally, the researcher will also ask if there are any variations in their food intake on bad versus good days and whether there have been any changes in eating habits compared to a month ago. Patients who are not admitted to hospital but come to the hospital on an outpatient basis, are being asked to fill out a 3-day food diary (2 week days and 1 weekend day). After 3 months the all patients will all fill out a 3-day food diary. During the 3 months,

participants will keep a logbook which they must record how much ONS was consumed daily for the total study period.
Individual protein requirement will be set at 1.5-1.9 g/kg FFM and energy requirements at WHO formula + surcharge up to 50% according to the Dutch guidelines of malnutrition and the ESPEN guidelines Clinical nutrition in surgery and cancer (6, 13, 23, 24).

For the check-in conversations the researcher will either make a phone call or have brief conversation at the hospital if the patient is already there for another appointment. The researcher will ask about any changes in body weight, discuss changes in the nutritional advice provided by the dietitian, their satisfaction about the ONS, ensure the patient is still correctly filling out the logbook, and address any questions or concerns related to the study.

Nutritional status will be measured by the Scored Patient-Generated Subjective Global Assessment (PG-SGA). The full PG-SGA has been validated among different patient groups and reported to be a simple instrument to use. Since the PG-SGA consists of a patient-reported part, the Dutch version of the PG-SGA will be used. This version is already available and considered comprehensible and easy to complete by patients, and comprehensible and relevant by professionals (20). One part is completed by the patient and another part by a specialist.

Body composition Fat mass (FM) and fat-free mass (FFM) will be measured using bioelectrical impedance analysis (BIA). The BIA device measures resistance in the body to an alternating current at 50kHz. FFM is then calculated with a formula that includes resistance, height, weight, sex and age. BIA represents a simple, non-invasive measure that takes only 5-10 min to perform.
Muscle thickness will be measured by muscle ultrasound with the Lumify (Philips) at the m. rectus femoris, vastus intermedius and m. biceps brachii.

Handgrip strength will be measured with the JAMAR handheld dynamometer in a standardized manner. Participants are asked to sit in an upward position with their elbows in a 90-degree angle and the wrist in a neutral position (thumb side upwards) and squeeze as hard as possible. Both hands will be measured 3 times, the highest value is used. Handgrip strength is a valid non-invasive method to measure muscle functionality and serves as a predictor for the overall muscle strength and change in nutritional status of participants.

Physical activity will be assessed using the questionnaire Short QUstionnaire to Assess Health-enhancing physical activity (SQUASH) at baseline and 3 months.

To measure Physical performance, the Short Physical Performance Battery (SPPB) and Timed Up and Go (TUG) will be used. The SPPB combines 3 separate tests, measuring gait speed, standing balance, and ability to rise from a chair. For the SPPB the scores of the 3 sub tests are all converted to a score range of 0-4, making the maximum score 12 points, indicating the best physical function (25). The TUG measures the time it takes for the patient to rise from a chair, walk comfortably 3 meters, turn around, walk back, and sit down. The patient may use their own walking aid and/or orthosis, but no physical assistance or encouragement should be given. This measurement is considered to be a reliable, cost-effective, safe, and time-efficient way to evaluate overall physical performance (26). The TUG and SPPB will be performed at baseline and 3 months.

Quality of Life will be evaluated using the EORTC-QoL-C30, a validated questionnaire for measuring quality of life. Questionnaires will be scored according to the procedures specified by the EORTC-QoL-C30 scoring manual (27).

Clinical outcome measures such as length of hospital stay, mortality and re-admissions within 3 months after hospital discharge will be determined retrospectively by using information from the EPR and confirmed by questionnaire with the participant since admissions from hospitals outside this study are not registered in an EPR. Complications within 3 months after hospital discharge will be determined by using information from the EPR. A complication is defined in line with the Dutch Association of Medical Specialists (FMS) as an unintended and undesirable event or condition during or following medical specialist intervention, which is so harmful to the health of the participant that change in medical treatment is necessary or that there is irreversible damage. Complications will be obtained from patients' medical records during hospital stay up to 3 months after baseline and coded as infectious, decubitus, surgical (non-infectious) complications and other (e.g., cardiopulmonary).

Qualitative interviews at T3

All participants of the pilot feasibility study will be approached by the researcher for an in-depth interview. Patients will be interviewed using a topic list. The topic list is based on the subscale 'Quality' of the validated 'measure of food access in hospitals' questionnaire (28), adapted to the use of ONS, and complemented with additional questions about sustainability. These interviews will be conducted using purposeful sampling based on sex, age, and patient group. We will continue these interviews till data saturation (no new information emerges) is reached. The estimated time for this interview will be set at 45 minutes.

8.4 Withdrawal of individual research participants

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

8.4.1 Specific criteria for withdrawal (if applicable)

Not applicable

8.5 Replacement of individual research participants after withdrawal

In this pilot feasibility study, participants will not be replaced after withdrawal, as both recruitment and drop-out rates are key measurements of feasibility.

8.6 Follow-up of research participants withdrawn from treatment

Not applicable

8.7 Premature termination of the study

In case the study is terminated prematurely, the investigators will notify the CCMO and the local ethical committee within 15 days, including the reasons for premature termination. Premature termination of the study is possible if the sponsor (i.e. Radboudumc), the government or the judging medical ethical committee (METC Radboudumc) decides to end the study. This could be decided when the study has led to unsafe or unethical situations.

9. SAFETY REPORTING

9.1 Temporary halt for reasons of research participant safety

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

9.2 AEs, SAEs

9.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a participant during the study, whether or not considered related to oral nutritional supplements intervention or study procedures. All adverse events reported spontaneously by the participant or observed by the investigator or his staff will be recorded.

9.2.2 Serious adverse events (SAEs)

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

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

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

The illness in this study population, consisting of cancer and lung diseases, cardiology-, cardiothoracic surgery- and orthopaedic conditions often progresses to a life-threatening stage due to the advanced nature of their disease. Similarly, prolonged hospitalizations are frequent among cancer patients due to the need for ongoing treatment, as well as among lung and cardiology/cardiothoracic surgery patients who may experience complications related to their disease and treatment conditions with no relation to the study interventions. Additionally, congenital anomalies or birth defects are not relevant to this study population, these conditions are not typically seen.

Therefore, the investigator will report all SAEs to the sponsor without undue delay after obtaining knowledge of the events, except for the following SAEs:

- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- is a congenital anomaly or birth defect

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

9.3 Follow-up of adverse events

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

9.4 Data Safety Monitoring Board (DSMB) / Safety Committee

Not applicable

10. STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences for Windows (version 29.0; IBM, SPSS Inc., Chicago, IL, USA) will be used for statistical analysis. Descriptive statistics will be used to explore the data and will be presented in tables and figures. Normally distributed data will be expressed as mean and standard deviation or as median, interquartile range, and minimum and maximum. Categorical data will be summarized by frequency or percentage.

10.1 Primary study parameter(s)

The primary analysis will explore the feasibility of a multicenter RNIT comparing plant-based and animal-based ONS in patients at risk of malnutrition with respect to the patient recruitment, drop-out rate, adherence, and the feasibility of study measurements.

10.2 Secondary study parameter(s)

Secondary analysis will provide the mean difference in protein intake i.e., total protein intake in g/kg FFM/d (based on dietary history) divided by 1.5-1.9 g/kg FFM/d, times 100%. In addition, the mean difference in energy intake i.e., total energy intake in kcal/d (based on dietary history) divided by WHO formula + surcharge up to 50%, times 100%. ANCOVA analysis will be used to estimate the effect of the group as independent factor on ‘mean difference in intake vs recommendation’ at T3 as dependent variable and T0 measurement as covariate. This is only meant as exploratory analyses and to be used for sample size calculations for the subsequent full-scale RCT.

The aim of the semi-structured interviews is to understand the experiences and perspectives of the patients using ONS regarding satisfaction (taste, smell, satiety), as well as their wishes and needs. Additionally, we are interested in their views of

sustainable nutrition. Therefore, these interviews will be approached from a phenomenological perspective. Qualitative analysis: all interviews will be audiotaped, and the records will be transcribed verbatim. Data will be analyzed using thematic analysis, starting with initial open coding to identify relevant data by minimal two independently working researchers. Codes will then be grouped into categories, the axial codes, and overarching themes will be identified. For this analysis, the software Atlas.ti will be used.

10.3 Other study parameters

Not applicable

10.4 Interim analysis (if applicable)

Not applicable

11. ETHICAL CONSIDERATIONS

11.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki in the current version of Helsinki, 2024 (29), guidelines for Good Clinical Practice (30), in accordance with the Medical Research Involving Human Subjects Act (Dutch: Wet medisch-wetenschappelijk onderzoek met mensen) (31), and in accordance with the General Data Protection Regulation (GDPR) (Dutch: Algemene Verordening Gegevensbescherming) (32).

11.2 Recruitment and consent

When during a consultation the dietitian decides that the patient needs at least 2 bottles of ONS and the patient is intended to use that amount of ONS, the dietitian checks eligibility for inclusion in the study based on the in- and exclusion criteria. When patients are eligible to participate in the study the dietitian will give the patient information about the study and ask permission to the patient whether they can be contacted by a researcher. If the patient agrees on being contacted by the researcher, the dietitian hands out the patient information letter, so they can read this in advance. The dietitian will inform the researcher which patients can be approached to participate in the study. Another way patients may receive ONS is through the nurse’s advice. In some cases, the nurse recommends that the patient take two bottles of ONS per day based on a MUST score of ≥2. The patient will continue using ONS during hospitalization and, upon discharge, will receive a referral letter to a dietitian in primary care. This ensures that patients continue to receive nutritional guidance at home. The researcher can check in the EPR which patients have an advice for ONS. If a patient is eligible to participate in the study, the researcher will contact the nurse, who will then

approach the patient to ask whether they are interested in receiving more information about the study from the researcher. The researcher will contact the patient as soon as possible. In this (phone) conversation the researcher further explains the study, and the patient can ask his/her questions. After this conversation the patient has 24 hours to decide if they want to participate or not. During this time, the patient will have the opportunity to consider their participation. If additional time is required for decision-making, this will be accommodated. Because the patient is at risk for inadequate nutritional intake, it is important that after the dietitian has advised the ONS, the patient also receives the drinks within a short period of time. That is why it is essential that we randomize the patient into one of the groups after 24 hours. If the patient is willing to participate, an appointment is made for the IC procedure. The IC form will be provided by the researcher and will be signed in a private room, prior to study initiation. Confidential processing of data and anonymity are guaranteed. Participants will have the opportunity to withdraw from the study at any time without the need to provide a reason.

11.3 Objection by minors or incapacitated research participants (if applicable)

Not applicable

11.4 Benefits and risks assessment, group relatedness

Participating in this study has no specific additional benefit. Generally, the use of ONS is expected to increase the energy and protein intake for patients, which in turn improves nutritional status. There are no potential risks associated with this research. Patients will receive ONS as part of their regular treatment, however, with participating in this study they will be randomized to receive either the plant-based or animal-based ONS. Both types of ONS are already available and used in hospitals. This study will not cause much additional burden on the patients in addition to their normal treatment as measurements are carried out during their hospital admission, or when possible, they are already present in the hospital for another appointment at the outpatient clinic. There will be 2 moments where measurements will be performed. The additional time they need to be available for the measurements of this study will be approximately 90 minutes for the baseline measurement and the measurements after 3 months. Within these 3 months, patients will be contacted by the researcher 1 month after the start (T1) and 2 months after the start (T2) for a ‘check-in’ conversation. For this conversation the researcher will either make a phone call or have brief conversation at the hospital if the patient is already there for another appointment. This conversation takes approximately 10 minutes. The participants are asked to perform 2 physical tests and complete questionnaires, which could be experienced as exhausting/ a burden.

11.5 Compensation for injury

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

The study protocol was reviewed by the Medical Ethical Committee of MUMC+, the Netherlands (METC 2025-0268) and Medical Ethical Committee Oost-Nederland (METC 2025-17931) and exempted from ethical review, according to the Dutch Medical Research Involving Human Subjects Act (WMO). Therefore, there is no insurance for the research participants.

11.6 Incentives (if applicable)

Patients will not receive any (financial) compensation for participation in this study.

12. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

12.1 Handling and storage of data and documents

Research data (including screening and enrolment files) will be stored in databases (Castoredc, Microsoft Excel, SPSS). Databases and audio recordings of the semi-structured interviews will be stored in protected workspace for researchers at the department of Gastroenterology and Hepatology and Dietetics at Radboudumc and the department of Dietetics of Maastricht UMC+. The coordinating researchers in this project group will have managing rights and receive access to the research data. Other project group members (dietitians or master/bachelor intern students collecting data) will have rights for data-entry. Audio recordings will be deleted after the transcript is written. All study documents will be stored in a file that is only accessible for the researchers who are directly involved in the study. Written data will be locked in a room, which is sealed by an entrance code or where a smartcard is needed. This written data will also be entered in the database Castor EDC. Within this data base every participant receives a study number. Both the subject identification list and the coded data will be stored separately on the password protected workspace. Only the study numbers will be used for study documentation, annual progress reports and research publications. The patients will be informed about the study number use of research data in the patient information folder. In the IC form, subjects will be asked permission to use their coded data. In addition, patients will be asked if data may be exchanged between Radboudumc and Maastricht UMC+ in the IC form. ICs will be stored in the EPR, separated from the other documents. Participants will also receive a copy from the IC, signed by themselves and one of the researchers. Both the written data and the entered data in Castor EDC will be stored for up to 15 years after the study. The data of this research may only be made public (open

access) in anonymized form. The handling of personal data follows the European Union General Data Protection Regulation, the Dutch Act on Implementation of the General Data Protection Regulation (UAVG), and the privacy regulations of the Radboudumc and Maastricht UMC+.

12.2 Monitoring and Quality Assurance

Because this study is a non-wmo study, there will be no monitoring.

12.3 Amendments

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

Non-substantial amendments will not be notified to the review committee, but will be recorded and filed by the sponsor.

12.4 Annual progress report

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

12.5 Temporary halt and (prematurely) end of study report

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

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

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

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

12.6 Public disclosure and publication policy

After analyzing all data, the goal is to present the results on (inter)national conferences and to publish the results in an international journal, independently on positive or negative outcome of the study. Also, the participants will be given insight into the general results, in the form of a summary. Individual results of the study will only be send to the participant if they specifically ask for this. This will be agreed with the sponsor in a contract.

13. STRUCTURED RISK ANALYSIS

13.1 Potential issues of concern

a. Level of knowledge about mechanism of action

ONS (i.e., energy and protein-rich drinks) are advised when habitual oral nutrition remains inadequate (75% of protein and energy requirements) (13). ONS have been proven effective in increasing total energy and protein intake, resulting in less complications and re-admissions, as well as improved body weight and physical functioning (14).

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

In previous studies, ONS have been proven effective in increasing total energy and protein intake(14). One previous study is done with another plant-based ONS, this study demonstrate that a ready-to-drink plant-based ONS is highly complied with, tolerated, acceptable and safe, and is effective at increasing total energy, protein and micronutrient intakes, body weight and BMI, and reducing malnutrition risk (33). Both ONS used for this study are available on the market and is already used in hospitals.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

Experiments in animals or using *ex vivo* human cell material will not answer the research question of this study. We will particularly investigate patients with cancer and lung diseases, cardiology patients, patients with cardiothoracic surgery, and orthopaedic patients to gain novel information that can be used for the development of nutritional strategies to reduce malnutrition risk. Thereby, an important part of this pilot feasibility study is the patients' satisfaction about the ONS.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Dietary protein-derived amino acids appear into the circulation and will be used by the entire human body (muscles, organs, skin). Plant-based medical nutrition contains high-quality proteins through the use of plant-based protein isolates. Plant-based protein isolate is purified protein that has been extracted from a plant-based food source. In this way, plant-based protein isolates can be absorbed by the body just as well as animal proteins. Furthermore, the calories in ONS will be used by the human body as energy fuel.

e. Analysis of potential effect

No potential adverse effects are known for the use of ONS.

f. Pharmacokinetic considerations

Not applicable

g. Study population

Patients from the oncology, lung diseases, cardiology, cardiothoracic surgery, and orthopaedic departments at risk for inadequate nutritional intake, age ≥ 18 years, treated at Maastricht UMC+ and Radboudumc.

h. Interaction with other products

No interactions have been reported.

i. Predictability of effect

High predictability of effect has been reported from earlier intervention studies mentioned above with regard to the use of ONS in patients at risk of malnutrition.

j. Can effects be managed?

Strict inclusion and exclusion criteria have been set for the inclusion of participants. The experimental trials will be performed at the nursing ward or in the clinical research unit, dependent on the mobility of the participant. During measurements, a researcher will always be present. The strict guidelines on how to respond in case of emergency within the nursing wards of the hospital will be followed.

13.2 Synthesis

The overall risk of participation in this study is negligible for patients. Consuming dairy products will form risks for people suffering from lactose intolerance, and consuming soy products will form risks for people suffering from soy allergy / intolerance. Therefore, these people will be excluded from participating in this study. Both types of ONS are medically available and are therefore safe for human consumption. All measuring procedures are completely safe and routinely being performed within the Radboudumc and Maastricht UMC+.

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