The impact of a home delivered meal service in the preoperative setting; a randomized study.

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Coordinating investigator/project leader	**Vera IJmker-Hemink** Diëtist-onderzoeker Afdeling Maag-, Darm- en Leverziekten, Diëtetiek en Darmfalen Radboudumc, Postbus 9101, HP 455 6500 HB Nijmegen
Principal investigator(s)	**Dr. G.J.A. Wanten, MD,** Maag-, Darm-, Leverarts Afdeling Maag-, Darm – en leverziekten, Diëtetiek en Darmfalen Radboudumc, Postbus 9101, HP 455 6500 HB Nijmegen **Dr. M.G.A van den Berg** Themaleider voeding/diëtist/ wetenschappelijk onderzoeker Afdeling Maag-, Darm – en leverziekten, Diëtetiek en Darmfalen Radboudumc, Postbus 9101, HP 455 6500 HB Nijmegen
Sponsor	***FoodforCare Foundation***
Subsidising party	***FoodforCare Foundation***
Independent expert (s)	**Dr. D.J. de Jong** Maag-, Darm-, Leverarts Afdeling Maag-, Darm – en leverziekten, Diëtetiek en Darmfalen Radboudumc, Postbus 9101, HP 455 6500 HB Nijmegen
Laboratory sites	*Nvt*
Pharmacy	*Nvt*

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department	**Prof. Dr. J.P.H. Drenth, MD,** Maag-, Darm-, Leverarts Afdeling Maag-, Darm – en Leverziekten, Radboudumc, Postbus 9101,HP 455 6500 HB Nijmegen	
Principal investigator(s)	**Dr. G.J.A. Wanten, MD,** Maag-, Darm-, Leverarts Afdeling Maag-, Darm – en Leverziekten, Radboudumc, Postbus 9101, HP 455 6500 HB Nijmegen	

Inhoud

SUMMARY

Background: Various approaches in the preoperative setting have demonstrated a positive effect on nutritional status and reduction of complications.

Objective: To investigate whether protein-rich nutrition of *FoodforCare* in the preoperative setting improves functional outcomes within 3 weeks in surgical patients, compared to usual care.

Study design: Randomized controlled trial

Intervention and procedure: Surgical patients are screened at the preoperative out-patient clinic for risk of malnutrition by nurses. In case of a score ≥ 1, which indicates a risk for malnutrition and a potential participant, patients are asked to participate. Participants randomized to the intervention group will receive the FoodforCare service in the preoperative setting for 3 weeks, which consists of five to six small protein and energy-rich meals. After an individual intake, the composition of the dishes will be tailored to the needs of the patient in terms of composition, diet, taste, flavor and portion size. Participants randomized to the control group will continue their usual diet in the preoperative setting for 3 weeks.

Main study parameters/endpoints: The primary outcome is the change in handgrip strength (between baseline and end of the intervention) between the 2 groups. Secondary outcomes include change in nutritional status, nutritional intake, patients' satisfaction, quality of life, length of stay and postoperative complications.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There are no additional tests or hospital tests necessary for the patient. This study will not confer any no additional risks. Food will be delivered within the expiration dates and the meals will be prepared according to the regular hygienic and food safety criteria that are valid. Possible serious reactions to the meals will be noted as SAE's.

1. INTRODUCTION AND BACKGROUND

Each year, approximately 1.4 million patients in the Netherlands are operated.(1) Adequate nutritional intake, mainly protein intake, before surgery is important to improve preoperative muscle strength and functional capacity. However, up to 40% of patients admitted to the hospital suffer from malnutrition and this further deepened during hospitalization(2), which is an independent risk factor for peri-operative morbidity and severe complications(3), ranging from increased muscle loss, to higher infection rates, delayed wound healing and subsequently a prolonged hospital stay.(4) Recent studies also reported a higher rate of postoperative complications in patients with respectively a low muscle mass, assessed using computed tomography (CT), or muscle weakness, defined by handgrip strength, preoperatively.(5, 6) These malnutrition-related complications have a major impact on hospital resources and healthcare costs.(7)

There are various types of approaches used in the hospital setting to optimize the nutritional status and improve functional capacity of hospitalized (surgical) patients.(8, 9) In enhanced recovery programs, which aims to ameliorate the response to surgery, various nutrition-specific aspects are included such as preoperative nutrition risk screening and carbohydrate loading, early feeding of normal food and inclusion of oral nutritional supplements prior to operation and for at least the first 4 postoperative days.(10) An adequate food service is another strategy to improve protein intake and thereby the nutritional status. An innovative hospital food formula, FoodforCare, is recently developed and implemented hospital-wide in the academic hospital (Radboudumc) in Nijmegen. This formula consists of small protein-rich dishes served 6 times a day, that aims at improving appetite and contributing to patients' wellbeing. Recent publication shows that FfC improves reached protein and energy requirements, compared to the standard food service.(11) Extension of the study period to the out-of-hospital setting is recommended to explore the effects of long-term exposure to this concept on clinical outcomes.

However, research has mainly focused on approaches in the postoperative period and during hospital stay, while evidence shows that this phenomenon might also be relevant in the preoperative setting.
A recent meta-analysis shows that preoperative nutritional support with parenteral nutrition improves clinical outcomes, such as length of stay and postoperative complications, in abdominal surgical patients at nutritional risk.(12) Another study shows that meaningful changes in postoperative functional exercise can be achieved with a prehabilitation program.(13) Studies on preoperative protein-rich diets are lacking.

Since FoodforCare has proven to increase nutritional intake in the hospital setting, we aim to determine whether protein-rich nutrition of *FoodforCare* in the preoperative setting improves functional outcomes within 3 weeks in surgical patients at risk for malnutrition, compared to usual care. We expect that this diet will have a beneficial effect on protein intake and therefore, on the nutritional status of the patients. Another positive effect might result from a reduction in postoperative complications.

2. OBJECTIVES

2.1 Primary objectives:

To investigate whether protein-rich nutrition of *FoodforCare* in the preoperative setting improves functional outcomes within 3 weeks in surgical patients at risk for malnutrition, compared to usual care. The primary functional outcome is determined as the difference in handgrip strength between baseline and the end of intervention.

2.2 Secondary objectives:

To investigate whether protein-rich nutrition of *FoodforCare* in the preoperative setting improves:

1. Functional status: Short Performance Physical Battery
2. Nutritional status (weight, Patient Generated Subjective Global Assessment (PG-SGA))
3. Protein- and energy-intake relative to requirements
4. Length of stay, number of readmissions and postoperative complications
5. Quality of life
6. Satisfaction of patients regarding food quality (and service when FoodforCare)

3. STUDY DESIGN

This is a randomized controlled trial (RCT). Given the nature of the intervention it is not possible to blind participants and investigators. This study will be conducted at the Radboud University Medical Center. This study will be directed according to the principles of the World Medical Association Declaration of Helsinki (64th WMA General Assembly, October 2013).

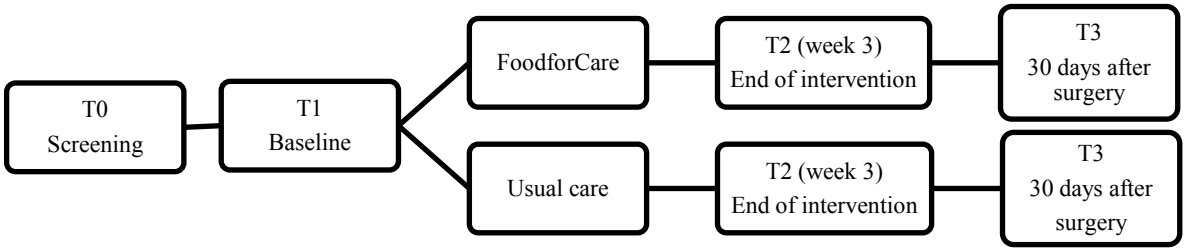
3.1 Recruitment

Surgical patients will be screened at the preoperative out-patient clinic for risk of malnutrition with the MUST (Malnutrition Universal Screening Tool) score by nurses. In case of a score ≥ 1, which indicates a risk for malnutrition and a potential participant, nurses will ask the participant whether they are happy to receive information about the study and will subsequently call the coordinated researcher. The researcher will conduct the initial screening and will inform the patient about the study. The patient will also be informed that participation is voluntary and withdrawal is possible at any time. The patient will receive an information leaflet with further information. A minimum of 24 hours later the researcher will contact the patient by telephone and ask whether he/she will participate in the study. After that, the informed consent form will be signed by the patient and send to the researcher, who will register the patient. The medical attending staff provided permission to approach individual patients.

3.2 Randomization and blinding

The researcher will randomize the patient by using a password-protected randomization service which is part of the clinical data management system ''Research Manager''. Participants are randomized to either the intervention or the control group, using block randomization, stratified for underlying disease and MUST score (MUST1 or MUST>1). After randomization, the system provides a trial participants number, who will be documented in a designated source document with the patient information. The study number and birth date will be listed on all study documents. Blinding seems not possible for the coordinating researcher, since one group will receive FoodforCare and the other group will receive no additional products. Whether blinding is possible for the researcher will be examined during the pilot study. In that case, patients will be asked not to tell the researcher in which group they are allocated. Patients have to be aware of the group allocation. Any important protocol modifications will be communicated with the Medical Ethics Committee.

Figure 1. Study design



4. STUDY POPULATION

4.1 Population

The study population consists of Dutch speaking patients undergoing surgery with a risk for malnutrition (MUST≥1), with oral intake, living within a radius of 40km from the Radboudumc. Patients on tube- or parenteral feeding, patients with renal insufficiency (MDRD-GFR < 60ml/min and/or proteinuria) or patients with impairment, which would prohibit the patient from full participation in the study, were excluded from the study.

4.2 Inclusion criteria

- 18 years or older
- MUST score ≥ 1
- living within a 40 km radius around Nijmegen/Veghel
- inclusion at least 4 weeks before surgery
- oral intake
- surgery: Urology, Orthopedics, colorectal and oesophagus.

4.3 Exclusion criteria

- renal insufficiency (MDRD-GFR (glomerular filtration rate) < 60ml/min and/or proteinuria)*
- underlying condition which makes it unpossible to perform hand grip strength

*proteinuria is defined in case of a protein creatinine ratio > 0.5g/10mmol or an albuminuria > 300mg/day.

4.4 Sample size calculation

The sample size calculation is based on the primary outcome of this study: the change in handgrip strength after 3 weeks between the groups. Based on literature and data from our previous study, patients will have a baseline handgrip strength of 28kg with a standard deviation of 5kg.(6) Assuming a difference of 2kg (7%) is a clinically relevant difference in favor of FoodforCare, we estimate that 209 patients are needed in order to obtain a power of 80% (two-tailed t-test, alpha 0.05). 251 patients should be included, assuming a drop-out rate of 20%. In order to improve the power significantly, we will make use of the ANCOVA test. By multiplying the number of patient with $(1-(\rho^2))$ a total of 228 patients will be needed. The correlation between the baseline and end of treatment (ρ) is estimated at 0.3, also because of the heterogeneity of the substantiated studies.

5. INTERVENTION

5.1 Name and description of investigational products

The FoodforCare at Home concept consists of five to six small protein and energy enriched meals that will be delivered twice a week. After an individual intake, the composition of the dishes will be tailored to the needs of the patient in terms of composition, diet, taste, flavor and portion size. Besides the meals, patients in the intervention group will also receive an information leaflet about the importance of protein during treatment and how to reach their protein requirements. The control group has no restrictions to their diet. The dishes are prepared by caterer Maison van den Boer, meeting the highest standards of nutrition and quality and served according to the regular hygienic and food safety criteria that are valid, and delivered twice a week by FoodforCare.

5.2 Summary of findings from clinical studies

Uit recente literatuur komt naar voren dat adequate preoperatieve voedingsondersteuning resulteert in betere klinische resultaten. Een recente meta-analyse uit 2015, bestaande uit gerandomiseerde, gecontroleerde trials, heeft gekeken naar het effect van preoperatieve voedingsondersteuning op klinische uitkomsten in ondervoede patiënten(14) Het betrof voornamelijk gastrointestinale chirurgie met parenterale therapie. Er werd geconcludeerd dat de ondersteuning superieur was voor wat betreft het verbeteren van klinische uitkomsten, onder andere in het verminderen van postoperatieve complicaties en verminderen van de opnameduur.

Een andere studie uit 2012 toonde aan dat preoperatieve voedingssupport (minimaal 7 dagen parenterale of enterale voeding) bij abdominale chirurgische patiënten met een verhoogd risico op ondervoeding (NRS 5 of hoger), leidde tot een significante vermindering in complicaties en opnameduur, ten opzichte van de controle groep.(15)

Daarnaast wordt er in het ERAS (enhanced recovery after surgery) protocol onder andere beschreven op welke manier uitkomsten na chirurgische ingreep kunnen worden verbeterd. Hierbij wordt gestreefd naar minimale stress rondom de operatie. Koolhydraat drankjes preoperatief lijken hierbij effectief in het verminderen van postoperatieve insuline resistentie.(9, 10)

5.3 Summary of known and potential risks and benefits

The food products of Maison van den Boer meet the highest standards of nutrition and quality and has therefore, no additional risk compared to usual products. All products will be served according to the regular hygienic and food safety criteria that are valid. Possible serious reactions to the products will be noted as SAE's. There are no additional tests or hospital visits necessary for the patient. Therefore, we do not expect any potential risk.

5.4 Dosages, dosage modifications and method of administration

The composition of the dishes are developed to enable maintenance and if possible improvement of the nutritional status of the patient. The aim is, therefore, to stimulate protein intake as much as possible with a protein intake of at least 1.2 gram per kilogram bodyweight per day. On average, this is equivalent to an intake of 90-95 grams of protein per person per day (assuming an average weight of 75-80 kg). Protein intake of 20-25 grams per meal would ensure optimal postprandial protein synthesis in the muscles.(14) This and other

information about the protein content of the FoodforCare products will be spread to the patients in order for them to make decisions that contribute to their protein requirements.

6. METHODS

6.1 Primary outcome

The primary outcome is the change in handgrip strength (between baseline and end of treatment) between patients receiving FoodforCare and patient on usual care (table 1).

Handgrip strength (HGS) is a valid non-invasive method to measure muscle functionality and serves as a predictor for the overall muscle strength, nutritional status and change in nutritional status of patients.(15) Importantly, studies have shown that impaired handgrip strength may be an indicator of increased mortality and morbidity, such as increased postoperative complications, length of stay, readmissions, and decreased physical status.(6, 16) HGS will be measured with the JAMAR meter on a standardized manner for the researcher.(17) Whether blinding is possible for the researcher will be examined during the pilot study.

6.2 Secondary outcomes

- Functional status: besides HGS, change in functional status will be evaluated with the Short Physical Performance Battery.
- Nutritional status: change in nutritional status will be assessed with the PG-SGA and measurements of body weight (table 1).(18) PG-SGA will be filled in by the patient and a member of the research team. Body weight will be measured on a calibrated weighting scale (type ..) in sober state. Relative weight changes will be presented as the percent weight change relative to the weight at baseline. Body Mass Index will be calculated.
- Nutritional intake: difference in nutritional intake (protein and energy) will be evaluated at every time point based on a 2-day food diary filled in by the patient. The food diary will be cross checked by a member of the research team and, if necessary, the patient will be called for clarification. The food items will be coded and calculated according to the Dutch Food Composition Table (NEVO, RIVM). During the pilot study, we will evaluate if a ‘’symptom diary’’ should be assessed.
- Length of hospital stay and readmission: reported from the medical record of the patients.
- Postoperative complications: reported from the medical record of the patients and classified using the Clavien-Dindo classification.(19) Grade of severity is based on the type of treatment for the specific complication. Infectious complications will be reported based on the definition of the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference.(20)
- Quality of life: change of quality of life will we assessed with the SF-36 questionnaire filled in by the patients. The Caregiver Reaction Assessment will be filled in by their caregiver.(21)
- Patient satisfaction:
    - Both groups will fill in a questionnaire with questions about their wellbeing and stress level regarding shopping and cooking of their meals.
    - In the intervention group, the Net Promoter Score (NPS) with additional questions will be used to assess patient satisfaction in the intervention group at time point 3. The NPS is determined by asking the question: ‘How likely is it

that you would recommend FoodforCare to a friend or colleague?'. The score ranges from 1-10 and patients can be grouped in 'promoters' (9-10 grading), 'passively satisfied' (7-8 grading) and 'criticasters' (0-6 grading). The NPS is finally calculated by subtracting the percentage of criticasters from the percentage of promoters.(22) Additional questions about satisfaction with respect to the food supply and logistics of FoodforCare will be answered by the patients to explain their score.

Both questionnaires are self-composed and based on validated questionnaires because there is no Dutch validated questionnaire available about a home-delivered meal service.

6.3 Other outcomes

- MUST: the Malnutrition Universal Screening Tool will be used at baseline and end of treatment (T2) to determine the risk of malnutrition.
- Adverse events: Possible adverse events including nausea, vomiting and gastrointestinal complaints will be identified by the ''symptom diary''. Unless we do not expect serious adverse events to occur, patients will be asked to contact a staff member and the researcher directly when adverse events occur. We will only report (serious) adverse events that have a possible causal relationship with the given food products till the end of the study. All AEs will be followed until they have abated, or until a stable situation has been reached.

Table 1. Measurements at each time point

	T0		T1	T2	T3
	Preoperative out-patient clinic	**Contact by telephone**	**Baseline**	**End of treatment**	**30 days after surgery**
Patient information	X				
Informed consent		X			
Randomization		X			
Handgrip strength			X	X	
Weight			X	X	
PG-SGA			X	X	
Nutritional intake			X	X	
Satisfaction				X	
SF-36			X	X	X
SPPB			X	X	X
Postoperative complication					X
Adverse events			X	X	X

6.4 Study procedure

A number of things will be set in motion after the patient signs the informed consent. As described earlier, the researcher will register the patient. If the patient is allocated to the intervention group, FoodforCare will be informed by the researcher. FoodforCare will take care of the delivering of the products and will have contact with the research assistants about the measurements. Before the start of the intervention, an individual intake will take place with the patient by FoodforCare. During this intake, the composition of the dishes will be tailored to the needs of the patient in terms of composition, diet, taste, flavor and portion size. These dishes will be delivered to the patients by FoodforCare every three days. Depending on the patient's wishes, the partner or caregiver of the patient can receive the same dishes. In case the patient is allocated to the control group, the research assistants are informed to perform the measurements at home at the given time points.

6.5 Withdrawal of individual subjects

Specific criteria for withdrawal

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

6.6 Replacement of individual subjects after withdrawal

During the inclusion period, additional patients will be included to be able to achieve the necessary number of patients in case of withdrawal of patients during the study.

6.7 Follow-up of subjects withdrawn from treatment

When patients withdraw from the study after time point 3, these data may (if authorized by the patient) be used for analyses.

6.8 Premature termination of the study

Situations in which the study should be terminated prematurely are not expected. Moreover, the use of 'usual care' and the FoodforCare products bring no additional risk to the patients. Therefore, we do not expect a large number of adverse events in either group.

7. PATIENT SAFETY

7.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

7.2 AEs, SAEs and SUSARs

7.2.1 Adverse events (AEs)

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

Our proposition will be to only register adverse events that have a possible causal relationship with the given food products. Examples of these events include gastrointestinal complaints and allergic reactions.

7.2.2 Serious adverse events (SAEs)

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

- 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;

- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Our proposition will be to only register serious adverse events that have a possible causal relationship with the given food products. Examples of these events include gastrointestinal complaints and allergic reactions, which cause the above mentioned.

7.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Not applicable for this study.

7.3 Follow-up of adverse events

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

8. STATISTICAL ANALYSIS

8.1 Descriptive statistics

Nominal and ordinal variables will be described using frequency tables, modus and medians. Continuous variables will be described in terms of means and confidence intervals or with medians and range, dependent on normality of the data.

Data will be analyzed using IBM SPSS version 22 for descriptive and statistical analyses. All analyses will be performed according to the intention-to-treat principle.

8.2 Primary study parameter(s)

The primary study parameter is the change in hand grip strength between baseline and the end of the interventions, in percentages, compared to the control and the intervention group. This difference in percentages is a continue variable and will be compared by using the ANCOVA test.

8.3 Secondary study parameter(s)

The change in the other parameters for nutritional status between baseline and the end of het intervention will be compared between the control group and the intervention group. The continue variables such as, the change in BMI, quality of life, functional status and patient satisfaction will be analysed by a t-test. The ordinal variable such as, the MUST score and the PG-SGA will be analysed with a Mann-Whitney-U test. The difference in number of patients with a complication will be analysed by a Chi-square test.

9. ETHICAL CONSIDERATIONS

9.1 Regulation statement

This study will be directed according to the principles of the World Medical Association Declaration of Helsinki (64th WMA General Assembly, October 2013). Additionally, is it in agreement with the Medical Research Involving Human Subjects Act (WMO) and other guidelines, regulations and Acts.

9.2 Recruitment and consent

Patients will be recruited through the department of Medical Oncology at the Radboud University Medical Centre in Nijmegen. All patients admitted to this department en those who meet the inclusion criteria are asked to participate in the study. This request will be discussed with the patient by the nurse or one of the researchers. Additionally, patients will receive a patient information letter with further information about the study. When everything is clear and the patient is willing to participate in the study, the informed consent will be signed. When a patient is enrolled in the study, a personal number is assigned by one of the researchers. The researcher documents the patients' data and the personal number in a designated protected document.

9.3 Objection by minors or incapacitated subjects

Not applicable.

9.4 Compensation for injury

There is a standard liability insurance available at the Radboud University Medical Centre for the study subjects. This is also written in the patient information letter. For the investigators there is also a liability insurance arranged at the Radboud University Medical Centre. In the proposal letter accompanying this protocol, we asked for release of a liability insurance for study subjects because this study includes usual nutritional care and meal service from FoodforCare which is already implemented in the medical centre. The patients will not be exposed to medical treatments during this study.

9.5 Incentives

Patients will not receive financial compensation for participating in the study. They will not have to pay additional hospital visits for this study and thus, they will have no additional travel costs or other costs. However, the intervention group will receive the meals and food products from FoodforCare for free. Due to the measurements that will be performed 3 months after the intervention period, it will not be possible to continue with the FoodforCare meals after this period. Once the effectiveness of FoodforCare at Home has been demonstrated, it is likely that the meals will become available for regular use.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

All study documents will be stored in the investigator site file. The informed consent forms will also be stored in Epic. The researchers will enter all data into the database of Castor by means of the study number with their personal password. Only the researchers who are directly involved in the study have access to this program. The key to the codes will be stored in a secure digital environment, so the privacy and anonymity of the patients is ensured. Both the written data and the entered data in Castor will be stored for up to 15 years after the study.

10.2 Monitoring and Quality Assurance

Looking at the directives of the NFU for on-site monitoring, the monitoring-class of the study is negligible. Minimum monitoring is indicated. The monitoring will be performed by an independent gastroenterologist according to the monitoring plan.

Monitor plan

Monitor Frequency	Once halfway the inclusion
Patient flow	Inclusion rate and drop-out percentage
Trial Master File/ Investigator File	Presence and completeness of research file
Informed Consent	100%
In-/exclusie Criteria	First 3 subjects, thereafter 10%
Source Data Verification	10%

10.3 Amendments

Not applicable with first version of the research protocol.

10.4 Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC in case the study takes longer than a year. In this report, information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit. For this study, this will be after the last measurement moment of the last patient.

In case the study is ended prematurely, the investigator will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10.6 Public disclosure and publication policy

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 results of the study. This will be agreed with the sponsor in a contract.

11. STUCTURED RISK ANALYSIS

11.1 Potential issues of concern

A risk analysis, in respect to the cooperation contract between Maison van den Boer and the Radboud University Nijmegen Medical Centre, will be described in the Aanbiedingnotitie to the Board of Directors and will also be contracted. For example, the risk of financial loss will be clearly described in this contract. This letter will also disclose that FoodforCare has no influence on publishing (positive or negative) results.

11.2 Synthesis

As described previously, we expect that this meal concept will have no additional risk to the patients. In daily practice, the dishes of FoodforCare are widely offered to all patients in the hospital. Matters such as patient safety and hygiene will be respected. In light of these arguments, it does not seem necessary to us to give a structured risk analysis.

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