

TEMPLATE RESEARCH PROTOCOL

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The impact of FoodforCare at home on quality of life of advanced abdominal cancer patients undergoing chemotherapy.

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: Cancer patients receiving treatment such as chemotherapy experience a variety of symptoms that interfere with their appetite and their ability to eat and enjoy meals. Several studies suggest that nutritional intake increases when the patient is satisfied about the quality of the meals. Therefore, adapting meals in a way that responds to these symptoms might be a good strategy to improve patient satisfaction, nutritional status and hence, quality of life. In this vein, we hypothesize that meals from FoodforCare at Home will contribute to the quality of life of advanced abdominal cancer patients undergoing chemotherapy when compared to usual care. Also, we expect that this strategy will have a positive effect on patient satisfaction, other nutrition-related issues, including nausea and vomiting, on nutritional intake per se and hence, on the nutritional status. Additional benefits might include reduced use of medication, especially anti-emetics.

Objective: To study whether FoodforCare at Home is superior to usual care with respect to quality of life in advanced abdominal cancer patients undergoing chemotherapy.

Study design: Randomized controlled trial

Study population: Advanced abdominal cancer patients undergoing chemotherapy, 18 years and older.

Intervention and procedure: Inclusion will take place at the department of Medical Oncology at the start of palliative chemotherapy. Patients will be randomly assigned to one of two groups before the start of the second cycle of chemotherapy. The intervention group will receive meals from FoodforCare at Home and the control group will continue their regular diet for 3 weeks between the 2nd and 3rd cycle of chemotherapy. The FoodforCare at Home meals will be delivered at the patient's home by research assistants or AYA's. These are Adolescents and Young Adults with cancer who are also trained to perform the measurements.

Main study parameters/endpoints: The main study parameter is quality of life of patients receiving FoodforCare at Home compared with patients receiving their usual diet. This will be evaluated by the EORTC-QLQ-c30 at all time points. The secondary endpoints are patient satisfaction, nutritional status, nutritional intake, performance scale, medication use, symptoms and quality of life of the partner/caregiver.

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 RATIONALE

Cancer patients receiving treatment such as chemotherapy often experience a variety of symptoms that interfere with their ability to eat and enjoy meals. These symptoms like loss of appetite, nausea and pain are referred to as nutrition impact symptoms [1]. Patients with several of these symptoms are more likely to experience a decline in nutritional intake [2]. Thus, reducing symptoms might lead to an improved nutritional intake. Furthermore, several studies suggest that nutritional intake increases when the patient is satisfied about the quality of the meals [3]. Therefore, adapting meals in a way that responds to these symptoms might be a good strategy to improve patient satisfaction and nutritional status.

Abdominal malignancies constitute a considerable proportion of all cancer types. Worldwide, the incidence of this type of tumors is 7.2 million and in the Netherlands alone this comprised more than 30.000 cases in 2015 [4]. Colon cancer is the most prevalent type of cancer within this group with an incidence of more than 15.500 in 2015 [5]. Furthermore, not unexpected, patients with abdominal cancer most frequently seem to experience symptoms that can interfere with eating [6]. For example, patients with gynecological tumors indicate to have some form of gastro-intestinal complaints in 70% of cases during hospitalization with loss of appetite, nausea and reduced taste being the most prominent features [7]. Gastro-intestinal side effects in colorectal cancer concern primarily abdominal fullness, nausea and vomiting [6, 8]. Besides, taste and smell alterations are well-known side effects of chemotherapy [9]. In the palliative stage, 70% of the patients experiences four or more diet-related symptoms [10]. It is important that special attention goes to symptom management in this stage because of the association between symptoms and quality of life [11, 12]. Accordingly, the main focus of palliative care is alleviating symptoms and increasing quality of life [10].

As a result of the symptoms caused by the disease and the treatment, palliative patients have a high risk for the development of malnutrition. This is due to decreased nutritional intake and disease-related metabolic changes resulting in a disturbed carbohydrate, fat and protein metabolism [10]. These metabolic disturbances are further exaggerated by the loss of appetite that is a common symptom in palliative patients [13, 14]. This interaction is called the anorexia-cachexia syndrome and can lead to cachexia [10]. Prevalence of cachexia varies between cancer types but the gastrointestinal tract has one of the highest rates with over half of all patients being affected [15]. In addition, cachexia is associated with reduced survival and decreased quality of life [16]. Therefore, maintaining and improving nutritional status is important during palliative treatment in order to improve quality of life. However, maintaining or improving nutritional status is only possible depending on the state of the disease [10].

Several studies show that patients often receive too little nutritional care which causes symptoms to worsen and frequently leads to hospitalization [17, 18]. Proper nutritional care and food provision contribute beneficially to maintaining nutritional status and quality of life of patients [3, 18]. Next to the fact that the meals should meet the nutritional requirements of the patients, other factors such as food quality and patients' satisfaction are important as well. In general, hospital food has a negative connotation due to the unfavorable contrast with homemade food [3, 19]. Patients value food quality and service quality the most and therefore, these are important predictors for patient satisfaction and quality of life [19, 20].

Furthermore, there is evidence of a positive association between patient satisfaction and energy intake [20].

There are various types of meal services that are used in the hospital setting and in the past years these have been optimized to the preferences and needs of hospitalized patients [21-24]. However, research has mainly focused on foodservice satisfaction in hospitals while this phenomenon might also be relevant for palliative patients at home, also in terms of time management. Studies on home delivered meal services mostly have been carried out in elderly people. In this population, improvements were seen in nutritional and functional status although most studies were cross-sectional with small sample sizes [25]. Few studies focused on patient satisfaction and quality of life [26, 27]. Frongillo et al. reported an overall satisfaction of 77% of the elderly who received home-delivered meals [26].

In the Netherlands, an innovative hospital food formula, FoodforCare, was recently developed and implemented hospital-wide in the academic hospital (Radboudumc) in Nijmegen. This formula consists of dishes with high nutritional values that aim at improving appetite and contributing to patients' wellbeing. FoodforCare makes use of small, frequent meals in order to reduce the risk of gastro-intestinal complaints and to reduce plate waste. There are studies stating that smaller portions are related to reductions in plate waste and an increase in energy intake [28-30]. In a recent pilot, so-called onco-proof products were offered to cancer patients. These products take account of the special consequences of the presence and treatment of the underlying condition for taste and smell and are rich in energy and protein. Patients who were submitted to this service described that they experienced lower levels of nausea when using these products compared to usual hospital meals. A tentative conclusion was formulated that this concept has a positive effect on the wellbeing and status of the patients.

It takes robust and well-designed studies to assess determine whether any meal service at home positively contributes to symptom management and quality of life in advanced abdominal cancer patients. The hypothesis of the present study is that FoodforCare at Home will be superior to usual care with respect to quality of life of advanced abdominal cancer patients undergoing chemotherapy. Furthermore, we expect that this meal service will have a beneficial effect on symptoms, patient satisfaction, performance scale, on nutritional intake and therefore, on the nutritional status of the patients. Another positive effect might result from a reduction in medication use (e.g. anti-emetics) and an improved quality of life of the partner/caregiver.

2. OBJECTIVES

Primary objective:

To study whether FoodforCare at Home is superior to usual care with respect to quality of life in advanced abdominal cancer patients undergoing chemotherapy.

Secondary objectives:

1. To reduce diet-related symptoms in these patients by using FoodforCare at Home compared to usual care.
2. To improve nutritional intake (adequate protein and energy intake) in these patients by using FoodforCare at Home compared to usual care.
3. To improve the nutritional status of these patients by using FoodforCare at Home compared to usual care.
4. To improve the functional status of these patients by using FoodforCare at Home compared to usual care.
5. To reduce medication use for the purpose of treating diet-related symptoms in these patients by using FoodforCare at Home compared to usual care.
6. To improve quality of life of the partners/caregivers of these patients by using FoodforCare at Home compared to usual care.
7. To improve patient satisfaction towards nutrition in these patients by using FoodforCare at Home compared to usual care.

3. STUDY DESIGN

A randomized controlled trial will be performed in palliative abdominal oncology patients at home. Inclusion will take place at the department of Medical Oncology at the start of palliative chemotherapy. The study is intended to be performed from March 2017 to July 2018. Patients will be randomly assigned to one of two groups before the start of the second cycle of chemotherapy because it is expected that FoodforCare at Home will make the largest difference during this cycle. The intervention group will receive meals from FoodforCare at Home and the control group will continue their regular diet for three weeks from the second cycle of chemotherapy until the next cycle of chemotherapy. Before the start of this study, a pilot study will be performed to determine whether the intervention is feasible in terms of logistics and delivery of the meals for example.

Measurements will take place at four time points during the study period i.e. before the start of chemotherapy, at the 2nd cycle of chemotherapy, at the 3rd cycle of chemotherapy and three month after T3 (figure 1). These measurements will be performed by AYA's/research assistants who will visit the patients at home. Time point 1, before the start of chemotherapy, will serve as the baseline measurement. At this moment, informed consent will be obtained and signed by the patient and the MUST score will be determined. Quality of life of patient and caregiver, nutritional intake, nutritional status, functional status and medication use will be assessed at all time points. For quality of life, the EORTC-QoL-C30 questionnaire will be filled in by the patients and the Caregiver Reaction Assessment by their caregivers. Nutritional status will be assessed using the handgrip strength measurement, the PG-SGA and performance scale by means of the Karnofsky score and the SPPB. Data on nutritional intake will be recorded using a 3-day food diary, which the patients will fill in by themselves. Medication use will be obtained from the patient's medical file. Additionally, during the intervention period, patients will record their symptoms using 'Utrecht Symptoom Dagboek' and medication use will be assessed by using a diary. At time point 3, patient satisfaction in the intervention group will be assessed by the Net Promoter Score with additional questions. An overview of the measurements can be found in table 1.

Figure 1. Flowchart of the study design of the FoodforCare at Home study.

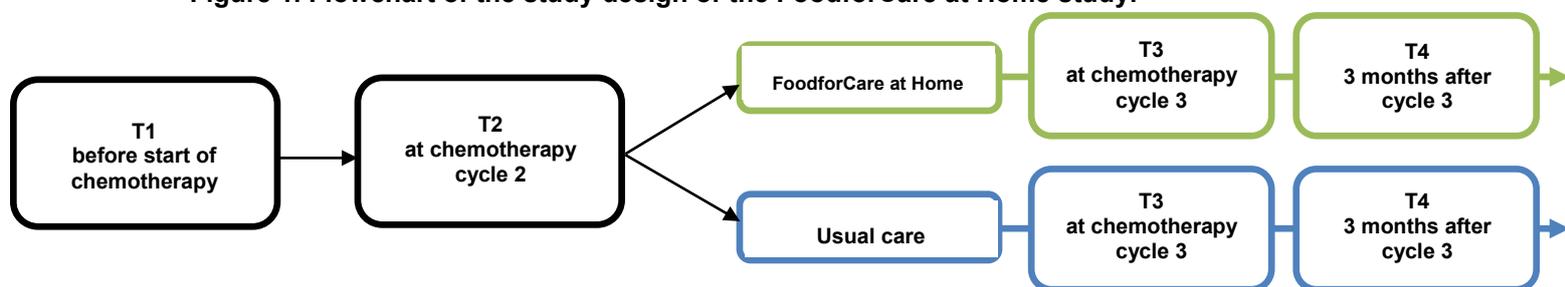


Table 1. Measurements performed at each time point during the FoodforCare at Home study

	Before chemotherapy	2nd cycle chemotherapy	3rd cycle chemotherapy	3 months after T3
Informed consent	X			
MUST score	X			
QoL patient	X	X	X	X
QoL caregiver	X	X	X	X
Nutritional intake	X	X	X	X
PG-SGA	X	X	X	X
Handgrip strength	X	X	X	X
Performance scale	X	X	X	X
Medication use	X	X	X	X
Patient satisfaction			X	

4. STUDY POPULATION

4.1 Population (base)

The study population comprises advanced abdominal cancer patients with gynecological malignancies or tumors in the colon. All patients scheduled for receiving palliative chemotherapy at the department of medical oncology (E30) at the Radboud University Medical Centre, Nijmegen (UMCN) will be recruited. In total, we expect approximately 200 palliative patients, with gynecological malignancies or tumors in the colon, to be scheduled for palliative chemotherapy at the UMCN annually. Taking a radius of 40 km from the UMCN into account, we expect that 40% will be outside this radius. This means that we expect approximately 120 patients to be able to be included in the study in a year.

Eligible patients will be requested to take part in the study after obtaining permission from the treating physician. This request will then be discussed with the patient, whenever possible in the presence of the caregiver, by the nurse or by one of the researchers. Additionally, the patient will receive a written leaflet with further information. The nurse or one of the researchers will ask the patient whether he/she has read the leaflet, whether the information is clear and whether he/she would like to participate in the study. After that, the informed consent form will be signed by the patient and the researcher will register the patient. Our intention is to consider an inclusion period of up to one and a half year.

4.2 Inclusion criteria

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

- age 18 years or older
- diagnosed with advanced colon or gynecological cancer
- receiving primary or secondary palliative chemotherapy according to a three weekly schedule
- living within a 40 km radius around the Radboud University Nijmegen Medical Centre
- written informed consent

4.3 Exclusion criteria

Patients will be excluded from participation in the study according to any of the following criteria:

- renal insufficiency (MDRD-GFR < 60ml/min and/or proteinuria)*
- dementia or any other condition which makes it impossible to fill out questionnaires correctly
- unable to understand or speak Dutch

- _____ depending on artificial nutrition in the form of Oral Nutritional Supplements, tube feeding or total parenteral nutrition

*proteinuria is defined in case of a protein creatinine ratio > 0.5g/10mmol or an albuminuria > 300mg/day. This is checked by default before the start of chemotherapy by the treating physician to decide whether or not the patient is eligible for receiving chemotherapy.

4.4 Sample size calculation

The sample size calculation is based on the primary outcome of this study: the EORTC-QoL-C30 questionnaire for quality of life. The primary outcome of this study is the difference in quality of life between the 2 groups at the start of the 3rd cycle of chemotherapy. Based on literature, advanced cancer patients with gynecological tumors and tumors of the colon have a mean score of approximately 60 points with a standard deviation of 22 points on the EORTC-QoL-C30 questionnaire. Assuming a difference of 10 points, on a scale of 0-100 points, is a clinically relevant difference in favor of FoodforCare at Home, we estimate that 76 patients are needed in each group in order to obtain a power of 80% (two-tailed t-test, alpha=0.05). Assuming a drop-out rate of 20%, this means a total of 180 patients. In order to improve the power significantly, we will make use of the ANCOVA test [31]. By multiplying the number of patients with $(1-(\rho^2))$ a total of 164 patients will be needed. The correlation between the baseline and follow-up outcome T2 (ρ) is estimated at 0.3.

5. INVESTIGATIONAL PRODUCT

5.1 Name and description of investigational product(s)

In a period of 1.5 year, 164 patients will be randomized into two groups. The intervention group will receive meals from FoodforCare at Home and the control group will continue their usual diet for 3 weeks. 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 every day by Maison van den Boer.

5.2 Summary of findings from clinical studies

The relevance of a good nutritional status in cancer patients undergoing chemotherapy has been described in several studies. Observational studies have shown that low nutritional status is associated with reduced survival and quality of life [12, 32]. Not many trials have been done into the effect of nutritional interventions on advanced cancer patients undergoing chemotherapy. Furthermore, the nutritional intervention mostly consists of Oral Nutritional Supplements (ONS), nutritional counselling or parenteral nutrition.

One trial in patients with gastrointestinal tumours undergoing palliative chemotherapy showed no effect of nutritional advice or nutritional supplements on quality of life. However, this study was small (N=68) and compliance to the supplements was low [33]. Another study from 2009 in advanced colorectal cancer patients undergoing chemotherapy found that supplementation with parenteral nutrition slows weight loss and improves quality of life. Patients in this study reached their energy and protein requirements 95-100% of all times [34].

To our knowledge, there is one other study that used regular foods and drinks as a nutritional intervention. The conclusion was that the products increased protein intake but no improvements in physical performance was seen. However, this study was performed in elderly people at home after hospital admission [35].

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 FoodforCare at Home dishes are developed to enable maintenance and if possible improvement of the nutritional status of the patient. Therefore, a number of basic principles are chosen which are described below.

The aim is to stimulate protein intake as much as possible in order to maximize protein synthesis during treatment. Protein intake of at least 1.2 g/kg body weight is recommended for cancer patients [36]. 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 [37]. 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 Study parameters/endpoints

6.1.1 Main study parameter/endpoint

Quality of life:

The main study parameter is the quality of life of advanced cancer patients using FoodforCare at Home. Quality of life will be evaluated using the EORTC-QoL-C30 at every time point. This is a validated questionnaire for measuring quality of life in palliative patients [38]. The global quality of life and the functional scales will be included as the main items in determining the quality of life of the patients. The symptom scales will be analyzed as secondary endpoint. Questionnaires will be scored according to the procedures specified by the EORTC [39].

6.1.2 Secondary study parameters/endpoints

For this study there are multiple secondary study parameters:

QoL caregiver:

The quality of life of the caregiver will be evaluated at every time point using the Caregiver Reaction Assessment (CRA). The CRA is a feasible and reliable instrument for determining the burden of caregivers of cancer patients which includes both negative and positive aspects [40].

Nutritional intake:

Nutritional intake will be evaluated at every time point based on a 3-day food diary filled in by the patient. The food diary will be cross checked by a dietician 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).

Nutritional status:

Nutritional status will be assessed using the handgrip method with the JAMAR handgrip measurer at every time point. Hand grip strength serves as a predictor for the overall muscle strength and functional status [41, 42] For reliable results, two consecutive measurements alternating both hands will be recorded with patients sitting in an upward position and the arm in a 90-degree angle. The validated Patient Generated- Subjective Global Assessment (PG-SGA) will also be used to determine the nutritional status and will be filled in by the AYA's/research assistants in consultation with the patient at every time point [43].

Performance scale:

The Karnofsky Performance Status Scale is used to summarize the ability of patients to perform daily activities and the degree of dependence on help to do so. This status is based on 11 levels and ranges from 0, indicating death, to 100, indicating no complaints or evidence of disease [44]. This score will be determined in consultation with the patient at every time point. Physical performance will also be assessed by the Short Physical Performance Battery (SPPB). This is a frequently used test to measure functional status and physical performance. It consists of three lower

extremity physical performance measures: standing balance, gait speed and chair rises (sit-to-stand) [45].

Medication use:

Medication use will be evaluated at every time point by obtaining information from the medical file of the patients. Information will be cross-checked by the researcher on doses and frequency of medication use. During the intervention period, medication use will be assessed by asking patients to log on a diary when they used which medication including dosage.

Symptoms:

To assess the number and the severity of symptoms experienced by the patients, they are asked to fill in the 'Utrecht Symptoom Dagboek' every day for 3 weeks during the intervention period. This is a diary based on the ESAS which consists of 12 symptoms which are frequently experienced by palliative cancer patients [46]. On a scale from 0 to 10, patients can score the severity of the symptoms with 0 indicating no symptom and 10 indicating the worst possible symptom.

Patient satisfaction:

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 [47]. Additional questions about satisfaction with respect to the food supply and logistics of FoodforCare at Home will be answered by the patients to explain their score. The control group will also receive a questionnaire about their wellbeing and way of shopping and cooking. Both questionnaires are self-composed and based on validated questionnaires because there is no Dutch validated questionnaire available about a home-delivered meal service.

During the pilot study, participants in the intervention group are asked to participate in an in-depth interview instead of the questionnaire. This interview will be led by one of the researchers. It will generate information about the home-delivered meal service so it can be improved when implemented in the RCT.

6.1.3 Other study parameters

Body weight:

Each patient's body weight will be determined at every time point. Relative weight changes will be presented as the percent weight change relative to the weight at baseline.

Height:

Each patient's height will be measured with a SECA ruler at the start of the study. From the measured body weight and height, BMI will be calculated by dividing body weight (kg) by the square of height (m).

Age, gender, type and doses of cytostatics, the number of chemotherapy cycles, education level, smoking and alcohol consumption:

Data on these variables will be determined at baseline by a questionnaire or from the medical files. The doses of the cytostatics will be determined at every time point.

Treatment toxicity:

Treatment toxicity will be monitored by the treating physician according to the Common Toxicity Criteria during the entire study period [48].

MUST:

The Malnutrition Universal Screening Tool (MUST) will be used at baseline to determine the risk of malnutrition.

6.2 Study procedures

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 AYA's/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 the AYA's/research assistants 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 AYA's/research assistants are informed to perform the measurements at home at the given time points.

6.3 Randomisation, blinding and treatment allocation

Patients will be randomized into two groups at the department of medical oncology in the Radboudumc. This will be performed by using the randomization program which is part of the clinical data management system 'Research Manager'. This validated web based data management system will be used during the entire study. The researcher will have a password to the randomization program. After randomization, a study number will be assigned to the patient. The researcher documents the patient information and study number in a designated source document. The study number and birth date will be listed on all study documents. The randomization will be stratified on tumor type and type of chemotherapy because of the possible effect on the primary outcome. This stratification reduces the risk of an uneven distribution of prognostic factors. We will not stratify for other characteristics; the exclusion criteria will contribute sufficiently to a homogenous patient population.

Blinding is not possible for the coordinating researcher, since one group will receive FoodforCare at Home and the other group will receive no additional products. Patients have to be aware of in which group they are in. Whether blinding is possible for the AYA's/

research assistants will be examined during the pilot study. In that case, patients will be asked not to tell the AYA's/research assistants in which group they are allocated.

6.4 Withdrawal of individual subjects

6.4.1 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.

6.5 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.

6.6 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.

6.7 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. SAFETY REPORTING

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.

Possible adverse events include: nausea, vomiting, gastrointestinal complaints. These events will already be identified by the EORTC-QoL-C30 questionnaire and the 'Utrecht Symptoom Dagboek'. Other side effects including severe (very rare) side effects are not expected to occur. However, it is important to monitor these side effects as well and therefore, the patient will be asked to contact a staff member and the researchers directly when side effects are present. 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

Repeated measures analysis by using mixed models will be performed to evaluate the course over time in quality of life and to analyze the difference between the two groups. The full maximum likelihood estimation will be used to assess the best fit of the model. In these analysis we will adjust for confounders in case of baseline imbalance.

8.3 Secondary study parameter(s)

The courses over time and the difference between the groups will also be analyzed for the secondary outcomes. The continuous variables like quality of life of the caregiver, nutritional status (hand grip strength, PG-SGA), nutritional intake and performance scale will be analyzed the same way as the primary outcome. The course over time and the difference between the groups in medication use like anti-emetics e.g. will be treated as a dichotomous outcome (yes/no) and analyzed by using the Chi-square test. The difference in patient satisfaction and severity of symptoms between the two groups will be analyzed using the independent samples t-test.

8.4 Interim analysis

No interim analyses will be performed in this study.

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.

Monitorplan

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. STRUCTURED 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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