NTNU

PRC European Palliative Care Research Centre

ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

Statistical Analysis plan (SAP)

Title: A randomised, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent / attenuate cachexia in advanced cancer patients undergoing chemotherapy.

The MENAC Trial

Administrative information

Sponsor name	Norwegian University of Science and Technology (NTNU) (non-commercial organisation)
Sponsor address	Department of Cancer Research and Molecular Medicine, Faculty of Medicine Norwegian University of Science and Technology PO Box 8905 Sluppen, NO-7491 Trondheim, Norway
Regional Ethics Committee of Central Norway approval no.	2014/1130
Trial title	A randomised, open-label trial of a Multimodal Intervention (Exercise, Nutrition and Anti-inflammatory Medication) plus standard care versus standard care alone to prevent / attenuate cachexia in advanced cancer patients undergoing chemotherapy
Short title (/Trial ID)	MENAC Trial
Trial registration number	ClinicalTrials.gov: NCT02330926
EUDRACT	2013-002282-19

SAP and protocol version

SAP version and date	v0.3 28.01.2022
Protocol version and date	MENAC-2019-01 version 22
Published protocol	Solheim TS, Laird BJA, Balstad TR, et al. Cancer cachexia: rationale for the MENAC (Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia) trial, *BMJ Supportive & Palliative Care*. doi: 10.1136/bmjspcare-2017-001440

SAP revision history

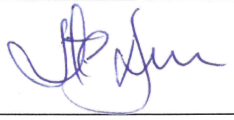
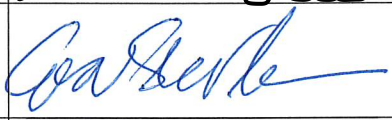
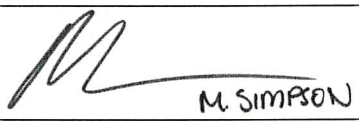
The SAP was developed based on the published protocol.

SAP version	Date changed	Comments
v0.1	20.01.2022	Initial SAP written by trial team.
v0.2	21.01.2022	Reformatted and expanded to follow recommendations set out by Gamble et al (*JAMA*. 2017;318(23):2337)
v0.3	28.01.2022	Clarified minor details in definitions and analysis strategy
v1.0	02.05.2022	Finalisation of subgroup analysis details (§5.2.3); minor clarifications of analysis strategy.

Abbreviations

aPG-SGA	Abridge Patient-Generated Subjective Global Assessment
AE	Adverse Event
AveS	Analogue Verbal Scale to estimate food intake
EORTC QLQ-C30	European Organisation for the Research and treatment of Cancer Quality of Life Questionnaire C30
EORTC QLQ-CAX24	European Organisation for the Research and treatment of Cancer Quality of Life Questionnaire CAX24
COX	Cyclooxygenase
CTU	Clinical trials unit
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
EQ-5D-3L	EuroQual-FiveDimension-Three Level Health status
ITT	Intention-to-treat
MENAC	Multimodal – Exercise, Nutrition and Anti-inflammatory medication for Cachexia
NSAID	Non-steroidal anti-inflammatory
NTNU	Norwegian University of Science and Technology
ONS	Oral nutritional supplement
PP	Per protocol
PROM	Patient-reported outcome measures
RCT	Randomised controlled trial
REK	Regional Etisk Komite (Regional Ethical Committee)
SAP	Statistical Analysis Plan

Signatures

	Name	Signature	Date
Chief Investigators	Professor Stein Kaasa (MD)		13/5-22
	Professor Marie Fallon (MD)		16/5/22
Statisticians	Professor Eva Skovlund		3/5-22
	Associate Professor Melanie Rae Simpson (MD)		2nd May 2022

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1. Introduction

This Statistical Analysis Plan (SAP) should be read in conjunction with the published trial protocol. (Solheim et al. 2018; Available at: http://dx.doi.org/10.1136/bmjspcare-2017-001440). The information available here provides a more detailed description of the "Statistical analysis" section.

The structure of this SAP follows the guidelines provided by Gamble et al. (2017) (Available at: https://jamanetwork.com/journals/jama/fullarticle/2666509) and the checklist available from: http://lctc.org.uk/SAP-Statement

All analyses will be reported according to CONSORT 2010 and ICH E9(R1) guidelines on Statistical Principles in Clinical Trials (Adopted September 1998, available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf).

1.1 Purpose and scope of the statistical analysis plan

This statistical analysis plan (SAP) describes the methods that will be used to analyse data collected as part of the MENAC trial for publication of the primary and secondary outcomes. This SAP does not cover exploratory analyses, although these will also follow the general principles set out here.

The aim of this document is, prior to unblinding of primary and secondary outcome data, to recapitulate the protocol, and establish details of the statistical analysis.

Any deviations from the analyses outlined in this SAP will be described and justified in the final report of the trial, including the inclusion of any analyses suggested by journal editors and referees. Modifications will be carefully considered and, as far as possible, will follow the broad principles set out here.

The details presented here shall not prohibit accepted practices, such as data transformation prior to analysis. When possible, such data management and modelling decisions will be undertaken prior to revealing the treatment allocation.

1.2 Background and rationale for the trial

Cancer cachexia is a syndrome of weight loss (including muscle and fat), anorexia and decreased physical function. The pathophysiology of cancer cachexia is a combination of reduced food intake and altered metabolism resulting from complex interactions between inflammation, hypermetabolism, neuro-hormonal changes, increased catabolism and reduced muscle/fat anabolism.

MENAC is an international multicentre, open, randomized phase III trial comparing a multimodal intervention (termed intervention arm) and standard cancer care versus standard cancer care alone (termed control arm) - ClinicalTrials.gov ID: NCT02330926 in patients receiving systemic anti-cancer therapy (SACT) for either lung or pancreatic cancer patients in the intervention arm will receive combined a) n-3 polyunsaturated fatty acids enriched oral nutritional supplements (ONS) and individual nutritional advice plus b) ibuprofen plus c) exercise (strength and endurance). This will be compared with the control arm.

1.3 Objectives and hypothesis

The primary objective of this trial is to prevent and /or attenuate the development of cachexia. The central hypothesis of this trial is that a multimodal intervention delivered during SACT in patients with lung or pancreatic cancer prevents the development and/or attenuates the effect of cancer cachexia. Direct effects from the cachexia intervention may be an attenuation of weight and muscle loss and, an improvement in physical activity and muscle strength.

As described in the protocol and in detail below (§5.1) the **primary outcome** will be body weight (kg) at endpoint (week 6). **Secondary outcome** assessment will include muscle mass assessed by CT L3 technique and physical activity level assessed by step counts using ActivPAL activity meter (§5.3). A number of **exploratory outcomes** are also described in the protocol and listed in Table 1 below (§5.5).

2. Study design

2.1 Trial design

As described, MENAC is an international multicentre, open, randomized phase III trial comparing a two parallel arms: multimodal intervention (termed intervention arm) and standard cancer care versus standard cancer care alone (termed control arm).

2.2 Randomization and treatment assignment

Patients consenting to participate in the trial are randomised and an ID-number is assigned to each patient automatically. Identifiable patient information will be stored at each participating trial site. Randomisation will be performed by a web-based randomisation system developed and administered by The Clinical Research Unit (Klinforsk), St Olavs Hospital, Trondheim, Norway. Random permuted blocks within strata were used. Baseline trial assessments are done before randomisation.

Patients will be randomised with a 1:1 ratio to either the intervention arm or the control arm and will remain in this until T2 (Figure 1). After T2 (endpoint assessments done) patients in the intervention arm will be offered the multimodal intervention but remain in the control arm.

Stratification factors are tumour type, stage of disease and country as detailed below:

- Non-Small Cell Lung Cancer (NSCLC) Stage III
- NSCLC Stage IV
- Locally advanced pancreatic cancer (stage III)
- Metastatic pancreatic cancer (stage IV)
- Non-operable cholangiocarcinoma (will be pooled with pancreatic cancer in analysis due to very few patients – see comment below)
- Country

A protocol revision was approved on 10.04.2017 where cholangiocarcinoma and small cell lung cancer (SCLC) were removed from the inclusion criteria. No small cell lung cancer patients were included before the amendment. Two patients with cholangiocarcinoma who had been included prior to this amendment will be analysed together with pancreatic cancer stage III or IV dependent on status of metastasis.

2.3 Determination of sample size

A clinically significant difference in weight (kg) between the two groups (trial arms) is defined as 0.5 SD. Based on the pre-MENAC pilot trial a difference of 2.85 kg between the groups (within group SD= 2.41) was demonstrated (p=0.004) (Solheim et al. 2017).

Detecting an effect size (ES) of 0.5 at endpoint week 6 (T2) using a two-sample t-test with power 0.9 and alpha 0.05 would require 90 patients in each of the trial arms (i.e. 180 in total). Based on current data from the Pre-MENAC pilot trial suggesting ~25% attrition (death or not assessed at week 6 (T2)), a recruitment of 240 patients will be required to obtain 90 patients in each arm.

On the basis of at least some positive interaction between the individual components of the proposed combination regimen, it would seem reasonable to estimate the ES to indicate a modest effect of at least 0.5 SDs and this would also represent a clinically important effect. The sample size calculation does not take into account contamination between trial arms. There is limited evidence of crossover from the pilot trial and the trial design is such that patients in the control arm are offered the intervention after 6 weeks to minimize this.

2.4 Framework

This trial is designed to establish the superiority of the multimodal intervention compared to standard cancer care in the prevention of cachexia:

- The primary null hypothesis is that the weight at T2 does not differ between the multimodal intervention and standard cancer care groups
- The primary alternative hypothesis is that the weight at T2 differs between the multimodal intervention and standard cancer care groups

There is only one primary outcome in this trial. The other efficacy analyses will be regarded as secondary or exploratory.

2.5 Statistical interim analyses

No interim or futility analyses are planned for the assessment of efficacy.

There will be an interim analysis after 50% and 75% of patients are recruited and completed assessment at week 6 (T2), to review the attrition, compliance and cross-over rates and assess the need to increase recruitment and or adapt follow-up strategies accordingly. A data monitoring committee (DMSC) will be set up to review confidentially the results of this interim analysis.

2.6 Timing of final analysis

End of trial is defined as 30 days after follow-up. However, date of death will be recorded 3 months after trial closure by sponsor. The analyses for all primary and secondary analyses will be performed once the data are clean and verified.

2.7 Timing of endpoint assessments

The timing of endpoint assessments is outlined in Table 1, below.

Trial baseline assessments (T0) will be before SACT starts and, and trial endpoint assessments will be done after a defined period of approximately after 6 weeks (T2) of SACT. A midpoint evaluation will be performed at week 3 (T1), and trial cessation follow-up is at 12 weeks (T3).

Choice of chemotherapy is not an eligibility criterion, and for some chemotherapy regimens the time between cycles are 3 weeks and for some 4 weeks. T2 is 6 weeks as most patients are expected to be on 3 weeks cycles and then experience 2 cycles before T2. T2 assessment is thus as close to week 6 as possible after baseline (not less than 40 days, and a maximum of 9 weeks/63 days), irrespective of trial arm. Although T2 is in principle at week 6, it may need to be delayed until before an upcoming treatment cycle to avoid registering side effects of anti-cancer treatment. As described below, the primary analysis will be performed on all participants regardless of when the T2 assessment occurred, whereas the per-protocol analysis will only include those whose T2 assessment fell within the pre-specified timeframe of 40 to 63 days.

Table 1. **Outcomes and trial assessments**

Outcomes and assessments		Baseline (T0)	Midpoint Week 3 (T1)	Endpoint Week 6 (T2)	Follow-up Week 12 (T3)
Patient demographics: Age, sex, height, ethnicity, living situation, smoking status, education and working situation		x			
Comorbidity: Charlson comorbidity index		x			
Cancer type and stage: TNM staging system		x			
Current medication: Type and dose		x	x	x	x
Body weight: Without shoes and with light clothes	Primary (T2)	x	x	x	x
Muscle mass: Cross-sectional area at L3 level from CT scans	Secondary (T2)	x		x	
Compliance with the interventions: Patient diaries and drug accountability			x	x	x
Drop out: Date and reason			x	x	x
Physical function:					
ActivPAL activity meter	Secondary (T2)	x		x	
Time-up and go test (TUG)	Exploratory	x		x	
Observer-based Karnofsky Performance Status (KPS)	Exploratory	x	x	x	x
Nutritional status and food intake:					
Patient-Generated Subjective Global Assessment (PG-SGA) questionnaire	Exploratory	x	x	x	x
24 h dietary recall interviews	Exploratory	x		x	
Analogue verbal scale (AveS) estimating dietary intake	Exploratory	x	x	x	x
Health related quality of life:					
European Organisation for the Research and Treatment of Cancer QoL Questionnaire – C30 (EORTC QLQ-C30)	Exploratory	x	x	x	x
Cachexia specific module (EORTC QoL-CAX24) as supplement to the EORTC QLQ-C30	Exploratory	x	x	x	x
Health status: EQ-5D-3L questionnaire (recommended by the National Institute for Health and Care Excellence for calculating quality-adjusted life years (QALYs))	Exploratory	x		x	x
Patient satisfaction with the intervention: Patient satisfaction with the components of the multimodal intervention using an adapted version of the EORTC IN-PATSAT32	Exploratory			x	x
Anti-cancer treatment: Tolerability of anti-cancer therapy (dose reduction, treatment delays, number of completed treatments as planned and adverse events)	Exploratory		x	x	x
Hospitalization: Number of admissions, duration and reason for the admission(s)	Exploratory		x	x	x
Blood samples for biobank: Serum, plasma, PAX tubes and full blood	Exploratory	x		x	
Biochemical blood analysis: Hemoglobin, leucocytes, CRP, albumin and creatinine	Exploratory	x		x	
Death: Date and place of death	Exploratory		x	x	x

3. Statistical principles

3.1 Confidence intervals and p-values

All efficacy and safety estimates will be presented with two-sided 95 % confidence intervals. Accompanying two-sided p-values will be calculated and compared to a 5 % significance level.

3.2 Adjustment for multiplicity

Although this study has a single primary analysis, we plan to adjust for multiplicity for the planned subgroup and secondary analyses to control the family-wise (or cumulative) type I error using Holm-Bonferroni method. Subsequently p-values will interpret as follows: if $0.01 < p < 0.05$ there may be an effect of the experimental intervention in the subgroup and secondary outcome analyses, but the evidence is weak; if $0.001 < p < 0.01$ there may be an effect; if $p < 0.001$ there is strong indication of an effect of the experimental intervention in the subgroup analyses and secondary outcome analyses.

3.3 Adherence, protocol deviations and protocol violations

3.3.1 Adherence

Information on adherence will be collected from patients for both the ibuprofen, nutritional and exercise aspects of the intervention in a daily check box style diaries to record:

- Use of ONS: no. of cans taken per day, measured by ½ cans
- Ibuprofen: no. of tablets taken per day
- Record of activity: completion of strength and aerobic exercise – no. of sessions as well as duration in minutes for aerobic exercise

The diary will be collected by the research assistants at the mid-point evaluation (week 3, T1) and end-point evaluation (week 6, T2).

Adherence to the nutritional or exercise aspects of the intervention are defined as follows:

- Drug: > 80% compliance with NSAID
- Nutritional: > 50% compliance with ONS; OR alternative ONS plus n-3 polyunsaturated fatty acids capsules
- Exercise: > 50% compliance with the total prescribed elements of aerobic and/or resistance exercise. Compliance with exercise is defined in terms of total duration which will be recorded in patient diaries and recorded independently by research staff.

3.3.2 Exclusions post randomisation

When ineligible patients are mistakenly randomized or withdraw before any trial baseline assessments and/or any multimodal intervention was given, the investigators will remove these patients from the trial. However, to ensure that the decision to remove such patients is unbiased and not influenced by events that occurred after randomisation (and may therefore be affected by whether patients are in the intervention or control arm), an independent adjudication committee blinded to randomization and outcome will systematically review each patient (Fergusson et al. 2002).

Responsibility

The adjudication committee must base its decisions on information that reflects the patient's status before randomisation or information about the process of withdrawal. Investigators should clearly state the number of patients randomised but not included in the primary analysis of data and explain the circumstances under which such patients were enrolled but excluded from the analysis.

Excluding randomised patients from the primary analysis may be legitimate when

- trial personnel made errors in the implementation of eligibility criteria, or
- patients withdraw before any assessment is conducted and never received any of the interventions

The adjudication committee evaluates and decide whether the patients in question safely can be excluded. The committee will meet when question concerning exclusion is raised from the trial office at NTNU. The committee will rapport on each individual reason for exclusion:

- Identification of patient
- Date of inclusion
- Reason for exclusion or keeping the patient in the trial
- Date for decision

All randomised patients will be included in the Consort Flow chart.

3.3.3 Protocol deviations

A participant will be considered to have deviated from the protocol if either they were not adherent to the drug, nutritional or exercise aspects of the intervention (detailed above §3.3.1) or the T2 assessment did not occur in the prespecified timeframe of 40 to 63 days (§2.7).

3.4 Analysis populations

3.4.1 Intention-to-treat population

The intention-to-treat (ITT) population will include all participants who were randomised.

3.4.2 Per-Protocol analysis set

The per protocol analysis set will include the subset of randomised patients with no protocol deviations in terms of adherence and timing of T2 assessment.

3.4.3 Safety analysis set

Safety analysis will include all randomised participants who commenced any aspect of the intervention.

3.5 Blinding

This is an open label trial, but primary and secondary outcomes will be assessed by an investigator blinded for the intervention arm.

3.5.1 Blinded statistician

The project administrators (TRB, BL) have been active in data acquisition and might theoretically understand from the clinical data from a given patient who the patient is. The statistician (MRS) and the trial physician (TSS) have, however, had no role in these analyses, and are still completely blind regarding randomisation group. To prevent bias, we will adhere to the following procedure: The Data Monitor (TRB) allocates a random number to patients in the intervention group and another to the patients in the control group. The code is written and stored safely, not accessible by the statistician. The statistician receives the dataset with these codes for the randomisation variable and carries out the primary analyses. When the statistician and trial management group have agreed upon the final analyses, they will be unblinded

4. Presentation of study population

4.1 Screening data, eligibility, recruitment and withdrawal

All participants admitted during the trial period will be randomised. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be used to summarise the number of participants as

shown in the published protocol. All exclusions will be identified in the CONSORT flow-chart along with timings and reasons for loss to follow-up where possible.

Key eligibility criteria: Diagnosis of lung cancer (non-small cell lung cancer (NSCLC stage IIIb-IV) or advanced pancreatic cancer, due to commence first or second line anti-cancer treatment, >18 years of age and Karnofsky Performance Score ≥70. No use of appetite stimulants and no major contraindications to NSAID (e.g. peptic ulceration). Written informed consent. A complete list of eligibility criteria are found in the protocol.

4.2 Baseline patient characteristics

Table 1 (above) summarises the participant demographic characteristics and baseline clinical status / characteristics which be presented. These demographics and baseline characteristics will be tabulated for each treatment arm and overall using descriptive statistics:

- Continuous variables: N, mean and standard deviation, and median and 25th and 75th percentiles as appropriate
- Categorical variables: counts and percentages for categorical variables.

5. Analysis

5.1 Definition of primary and secondary outcomes

5.1.1 Primary outcome

The primary outcome is body weight (kg) at the endpoint (T2). The efficacy of the outcome will be presented as the difference in change in body weight from baseline between the intervention and control arm.

5.1.2 Secondary outcomes

The efficacy of the intervention on secondary outcomes will be measured as differences between study baseline (T0) and endpoint (T2) in the two study arms for muscle mass and physical activity.

Muscle mass will be assessed using cross-sectional imaging of computer tomography (CT) scans taking an axial image at the 3rd lumbar vertebra (L3). Total muscle cross-sectional mass will be recorded in square centimetres (cm^2). Technical details to standardised the CT images and quantification of muscle mass are described in the protocol document. Muscle mass will be calculated at baseline and at T2.

Physical activity as a secondary outcome will be assessed as average daily step counts over a 7-day period as recorded by an ActivPAL activity meter at baseline and at T2. Other measures of physical activity are included as exploratory outcomes.

5.2 Analysis of primary outcome

The primary efficacy analysis will compare the primary outcome (weight, kg) at endpoint (T2) in the intervention and the control groups, using fixed effect multiple regression models.

The primary analysis will be performed in patients in the ITT population and with the primary outcome completed, including those whose weight was measured outside of the intended timeframe of 40 to 63 days. Stratification factors and baseline values of the outcome variable will be included as covariates. Estimated mean difference in change in weight between the intervention and control arms will be presented along with 95 % confidence interval. A type I error of 5% (a p-value <0.05) will be regarded as statistically significant.

The sample size calculation was based on the pragmatic and conservative approach of using two-sample t-test to compare the post treatment weights in the intervention arms. The results of a two-

sample t-test will therefore also be presented for the sake of completeness, however the statistical approach outlined above will provide greater precision and statistical power.

5.2.1 Assumption checks and sensitivity analyses

The assumptions for linear regression will be performed, assessing normality in the residual variables and evidence of heteroskedasticity across predictor variables. If the primary outcome has a substantially skewed distribution, bootstrapping will be considered to obtain robust estimates of the confidence intervals.

Sensitivity analyses will be used to explore the robustness of the analyses. For example, additional analyses including the following potentially prognostic covariates will be undertaken: CRP, (CRP≤10, CRP> 10mg/l), Albumin (≤35, > 35g/l), Karnofsky performance scale (KPS) (≤70, >70) and Weight loss (WL ≤10%, WL>10% in the previous 6 months to baseline (T0)).

In additional sensitivity analysis, the effects of intervention over time will also be explored using linear mixed models to account for the dependency of the observations from T0, T1 and T2. Here all consenting patients with at least one measurement of the outcome variable will be included. Covariates as listed above will be considered.

5.2.2 Missing data

If a large proportion of patients (>20%) have a missing outcome on T2, multiple imputation as well as imputation of missing values according to different scenarios/assumptions may also be considered. For multiple imputation we will impute expected values at the six-week timepoint (T2), generating 10 different datasets with imputation based on a regression model. In this model we will include the following factors if they are statistically significant predictors of the outcome or of having a missing answer ($p<0.05$ in a univariate model and less than 5% missing on the variable in question): baseline values of the primary and secondary outcome variables, the stratification factors (cancer diagnose/stage and country), sex, age type of anti-cancer treatment, CRP, albumin, KPS and weight loss. Only variables that are strong predictors of the outcome or of missingness will be included in the model.

5.2.3 Subgroup analyses and treatment effect heterogeneity

Secondary analysis will examine if the previously mentioned prognostic factors influence the efficacy of the intervention on the primary outcome in addition to age, sex, and diagnosis category. Specifically, the efficacy of the treatment will be explored in each of the following groups:

- Inflammation: categorised as CRP ≤ 10mg/l or CRP > 10mg/l
- Weight loss in the previous 6 months to baseline: ≤ 10% or > 10% at baseline
- Albumin: ≤ 35 or > 35g/l
- Karnofsky performance scale (KPS): ≤ 70 or > 70
- Age (categorise < 70 or ≥ 70 years)
- Sex: male or female
- Diagnostic category: Non-Small Cell Lung Cancer (NSCLC) Stage III, NSCLC Stage IV, locally advanced pancreatic cancer (stage III), or metastatic pancreatic cancer (stage IV) / non-operable cholangiocarcinoma

The subgroup analyses will be presented collectively in a Forest plot. If there are not sufficient numbers within the subgroup, we will reconsider the categorisations. Additionally, treatment effect heterogeneity will be assessed in separate regression models which include an interaction term between each of the above subgroups and treatment allocation.

5.2.4 Additional analyses

As a sensitivity analysis, the primary analysis will also be performed on the per protocol population. Additional analyses may be considered to examine the effect of intervention in the previously defined subgroups (§5.2.3) for the primary outcome in the per protocol population.

The per protocol population is defined based on a minimum level of adherence to all aspects of the multimodal intervention, however we recognise that different aspects of the multimodal intervention may have a greater effect that others. Additional exploratory analysis may therefore be considered in order to examine the effect of the intervention depending on adherence to the individual aspects of the multimodal intervention, both separately and in combination.

5.3 Analysis of secondary outcomes

Secondary efficacy analyses will be performed based on the participants in the ITT population and with complete information at follow-up for the respective outcomes. For each secondary outcome, the difference between study arms at the endpoint (6 weeks) will be estimated again using the corresponding baseline values as covariates (effectively, assessing change from baseline).

Sensitivity analyses will be used to explore the robustness of the secondary analyses. These will include analyses using all and no covariates, and linear mixed models as described for the primary efficacy outcome.

5.3.1 Additional analyses

As for the primary outcome, additional analysis may be considered to examine the effect of intervention on the secondary outcomes in both the per protocol population and based on the previously defined subgroups (§5.2.3).

5.4 Analysis of safety outcomes

A summary of toxicity by intervention arm is reported as grade of the following events: pain, constipation, fatigue, dyspepsia, mucositis, anorexia, nausea, vomiting, infection, neutropenia, thrombocytopenia, oedema, ascites.

All adverse events (AE) are assessed by CTCAE v4.0 on a 5-point level, from absent (0) to high (4). All registered AEs are listed by intervention arm and patient.

Number of patients experiencing toxicity/AE between baseline and T1 and between T1 and T2 will be presented descriptively per intervention arm.

Cumulative number of serious adverse events (SAEs) that have been reported during the reporting period organized by System Organ Class (SOC) will be reported by intervention arm.

5.5 Analysis of exploratory outcomes

A number of exploratory outcomes are identified (see Table 1). Exploratory efficacy analyses will be performed on the per-protocol population. Appropriate regression models will be used to compare these outcomes between the treatment arms and including baseline values where these are recorded. For outcomes recorded at multiple timepoints, we plan to use multilevel regression modelling and include an interaction term between treatment arm and timepoint to allow for differing effect of treatment depending on time.

5.6 Statistical software

STATA version 17 or above will be used for data analysis.

6. References

Fergusson et al, Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis, BMJ. 2002 Sep 21; 325(7365): 652–654.

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