STATISTICAL ANALYSIS PLAN
FIDURA (dietary FIber intake DUring pelvic RAdiotherapy)

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Table of Contents

1. INTRODUCTION

1.1. Background and rationale

Most, if not all, patients receiving pelvic radiotherapy will develop permanently changed bowel habits as a result of radiation exposure to the bowels [1,2]. As the tissue is exposed to ionizing radiation an acute inflammation is triggered, followed by a low-grade inflammation, ischemia and fibrosis [3]. The acute symptoms will subside, but others may persist and new ones develop years to decades after the cancer treatment, severely affecting quality of life [4]. Five symptom clusters (syndromes) can be distinguished years after pelvic radiotherapy [5]. The symptoms are related to a continuous urgent need to defecate (fecal-urgency syndrome), fecal leakage (fecal-leakage syndrome), leakage of mucus (excessive mucus discharge), uncontrollable flatulence (excessive gas discharge) and anal bleeding (blood discharge) [5]. The fecal-urgency syndrome is one of the most common and problematic syndromes among cancer survivors after radiotherapy [6]. There is limited data to establish the underlying mechanisms for the five syndromes and there is a lack of efficient preventative strategies and treatments [7].

A handful of studies in human and animals suggests that dietary interventions may affect both acute and chronic symptoms, but the evidence is weak [8]. Today, there are no established, evidence-based, dietary recommendations for patients undergoing pelvic radiotherapy or pelvic cancer survivors [9]. Wedlake *et al.* provided some support that a high-fiber diet (16 g non-starch polysaccharides/day) may improve intestinal health one year after pelvic radiotherapy [10]. Dietary fiber, primarily found in whole grain products, vegetables, and fruit, may prevent radiation-induced injury of the intestinal wall. This is likely to be, at least in part, due to the production of short chain fatty acids that are used as an energy source by the colonocytes and contribute to an improved intestinal integrity [11,12]. Nonetheless, both in Sweden and internationally, many patients are advised to reduce intake of dietary fiber during pelvic radiotherapy [10,13]. This advice probably stems from the notion that fiber intake might cause bloating and increased discomfort, and thereby exacerbate the acute symptoms. In FIDURA (dietary Fiber Intake DUring Radiotherapy) a randomized, placebo-controlled, double-blinded clinical trial, we collect data to develop evidence-based nutritional recommendations with regards to dietary fiber intake for patients undergoing pelvic radiotherapy and irradiated pelvic cancer survivors.

1.2. Objectives

1.2.1. Primary Objectives

There are two co-primary objectives:

Primary Objective 1: Investigate if the addition of 6 g psyllium husk, compared to placebo, will reduce the level of C-reactive protein (CRP) measured four weeks after the end of radiotherapy.

Primary objective 2: Investigate if the addition of 6 g psyllium husk, compared to placebo, will reduce the level of Urgency Syndrome measured one year after the end of radiotherapy.

1.2.2. Secondary Objectives

Secondary Objective 1: Investigate if the addition of 6 g psyllium husk, compared to placebo, will affect the level of Leakage Syndrome, measured one year after the end of radiotherapy

Secondary Objective 2: Investigate if the addition of 6 g psyllium husk, compared to placebo, will affect the level of Excessive Gas Discharge Syndrome, measured one year after the end of radiotherapy

Secondary Objective 3: Investigate if the addition of 6 g psyllium husk, compared to placebo, will affect the level of Excessive Mucus Discharge Syndrome, measured one year after the end of radiotherapy

Secondary Objective 4: Investigate if the addition of 6 g psyllium husk, compared to placebo, will affect the level of Blood Discharge Syndrome, measured one year after the end of radiotherapy

2. STUDY METHODS

2.1. Trial design

In this triple-blind, superiority, parallel study, participants were automatically randomized to one of two groups through a study-specific database. Participants received blinded capsules containing either psyllium husk or placebo, and all participants were given individualized dietary advice e.g., to daily eat at least 16 g of dietary fiber (Figure 1). During the study, the participants filled out three questionnaires at a digital application and donated four blood samples and five fecal samples (Figure 1). Repeated telephone follow-ups were made to ensure that the participants did not experience aggravated symptoms owing to study intervention.

Patients with gynecological cancer and prostate cancer scheduled for curative pelvic radiotherapy were recruited from the oncology clinic, urology clinic, or gynecological clinic at Sahlgrenska University Hospital in Gothenburg or Skåne University Hospital in Malmö and Lund.

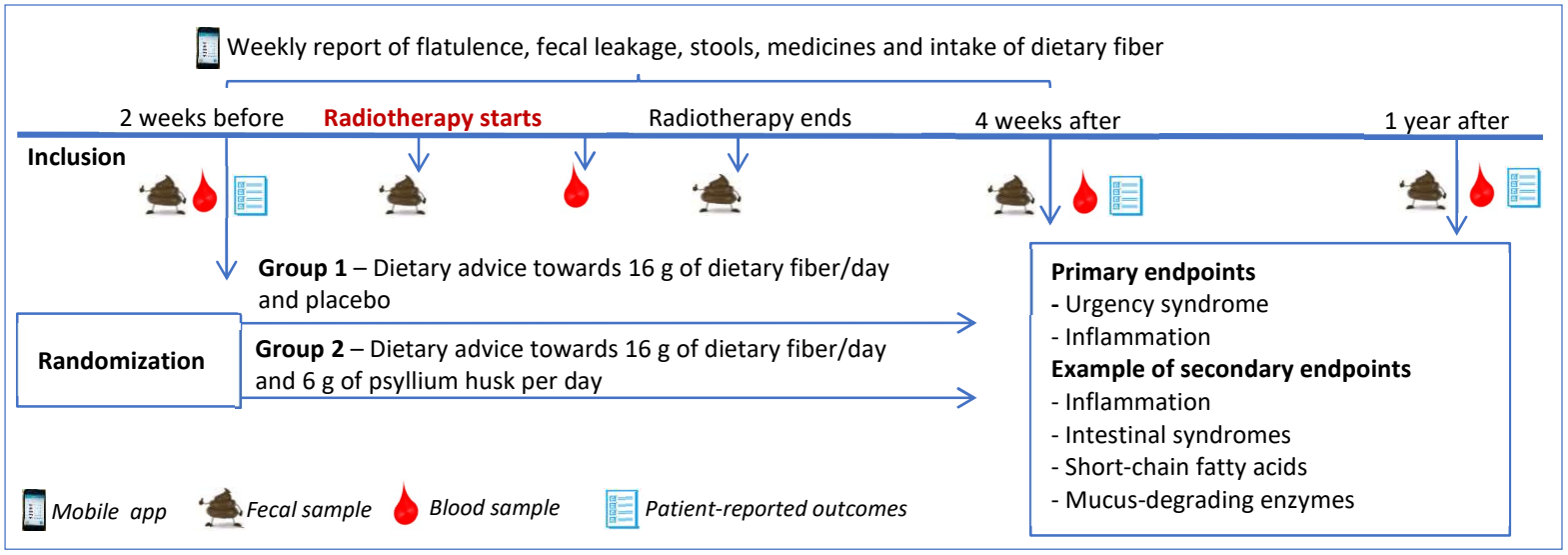

Figure 1. The study design of FIDURA (dietary FIber intake DUring pelvic RAdiotherapy)

The two groups received the same information but were provided with different capsules. The active capsules include a fiber supplement (Finax® psyllium husk) which is rich in gel-forming soluble fiber, whilst the matched placebo (maltodextrin) does not include any fiber. The participants were instructed to consume 15 capsules per day (which include 6 g of psyllium husk, equal to 5g dietary fiber). Instructions were given how to ingest the capsules (enough fluid intake, mix with drinks or foods, and avoid ingest together with drugs) and gradually step up the intake during seven days.

2.2. Randomization

Simple randomization was used to allocate participants 1:1 to either placebo or fiber capsules.

2.3. Power

The original planned sample size was 500 patients, with 250 in each randomized arm. Trial recruitment was stopped when the PI sadly died in July 2023. At that point a total of 354 patients had been recruited (190 randomized to one arm and 164 to the other arm). The original sample size calculation is shown below.

In order to estimate the power of the Mann-Whitney to detect the relative effect of the two fiber regimes a simulation study was undertaken, modeling the potential effect as a shift in the empirical distribution of the factors scores, interpreted as syndrome intensities, associated with the Urgency Syndrome among gynecological cancer survivors. A selection of the range of theoretically relevant shifts was studied at 101 equidistant locations, including the zero shift. At each such point 1000 samples of sizes 250 were drawn with replacement from the original and shifted distributions, and a Mann-Whitney test was performed and evaluated at the 0.05 level. Once again at each such point the fraction of such tests suggesting

a rejection of the null hypothesis was recorded. These fractions were finally used as the basis of the loess smoothed function found in Figure 2. An investigation of the function suggested that a power of 80 % is attained at a shift of 1.06.

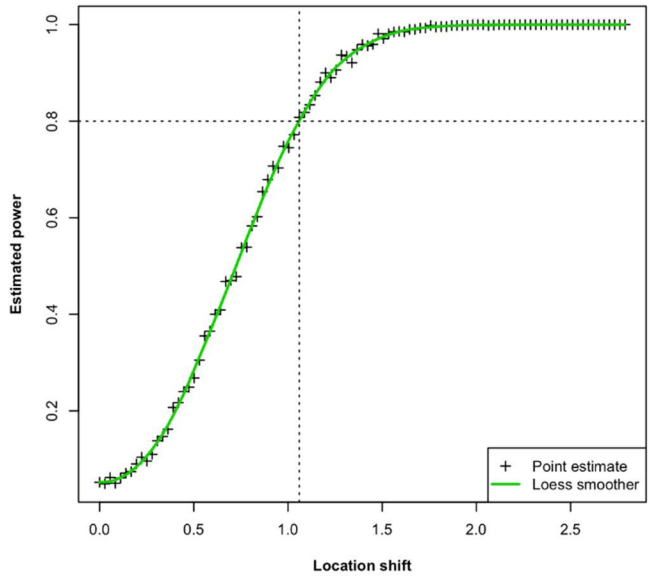

Figure 2. Simulated power function with respect to location shift.

The study was stopped earlier, therefore a power calculation was performed on the final dataset:

Power calculation: For both primary outcomes, we have recalculated the power based on an assumed dropout rate of 10% at 4 weeks after radiotherapy and 15% dropout rate at the one-year follow-up. Hence the power is based on sample sizes of 318 for CRP at 4 weeks and 300 for Urgency Syndrome at 12 months. We have used an alpha of 0.05 for both comparisons. For CRP at 4 weeks, following the results reported in Pal et al [14] we assume that in the control group CRP will increase by 400ng/mL, and that in the intervention group it will decrease by 700ng/mL, with a common SD of 3100. With these assumptions, we will have 88% to detect a difference. For Urgency Syndrome at 12 months, based on results we published in 2019 [15] we assume that at baseline the mean syndrome score will be -2.1 (SD=2.8) in both arms, but will increase during the study to 1.1 (SD=4.6) among the control group. Assuming that the intervention mitigates half of this increase, we estimate that in the intervention group, the mean urgency syndrome score will increase to -0.5 (SD=4.6). Hence the change in the two groups will be 3.2 and 1.6, respectively, with a common SD of 3.6. Under these assumptions, we will have 97% power to detect a difference.

2.4. Framework

This is a superiority trial, with the aim of showing that the addition of dietary fiber will improve patient symptoms, compared to the control group.

2.5. Statistical interim analysis and stopping guidance

No interim analysis was planned nor performed. The trial stopped recruitment early following the death of the principal investigator. At that point 354 people had been randomized. Follow up visits are ongoing, final visit will take place in August 2024.

2.6. Timing of final analysis

When all participants have finished their one-year follow-up.

2.7. Timing of outcome assessment

Baseline data on CRP levels and urgency syndromes were collected two weeks prior to the start of radiotherapy, with outcome data gathered at multiple time points: immediately before, during, four weeks, and one year after treatment. The collection of data is presented in Figure 1. The primary CRP endpoint is measured at four weeks after radiotherapy. The primary urgency endpoint is measured one year after radiotherapy.

3. STATISTICAL PRINCIPLES

3.1. Confidence intervals and p-values

95% confidence intervals will be applied and P values <0.05 will be considered statistically significant.

3.2. Adherence and Protocol deviations

We will report the proportion of capsules consumed by each participant less than/more than 80 percent of capsule intervention. Adherence will be measured by capsules given subtracted by capsules returned.

	Control arm (N=xx)	**Intervention arm (N=xx)**
Percentage consumed: median (IQR)		
<80%	n (%)	n (%)
≥80%	n (%)	n (%)

3.3. Analysis population

1. Intention-to-treat. This will consist of all randomized participants who initiated at least one task in the study, who will be analyzed according to their original assignment.
2. Per-protocol. Participants who consumed at least 80 percent of the capsules.

4. TRIAL POPULATION

4.1. Screening data

The table will be completed.

	Included (N=xx)	**Excluded (N=xx)**
Age: median (IQR)	xx (xx - xx)	xx (xx - xx)
Sex		
Female	xx (xx%)	xx (xx%)
Male	xx (xx%)	xx (xx%)

4.2. Eligibility

Inclusion criteria:

- Patients with gynecological cancer and prostate cancer scheduled for curative pelvic radiotherapy.

Exclusion criteria:

- preoperative stoma as determined by the treating physician to prevent participation.
- swallowing difficulties or ileus condition as determined by the treating physician to prevent participation.
- cognitive dysfunction as determined by the treating physician to prevent participation.
- need for an interpreter to communicate in Swedish.

4.3. Recruitment

We will complete a CONSORT flow diagram to show number of participants recruited and the number of (and reasons for) withdrawals.

4.4. Baseline patient characteristics

The table will be completed.

Characteristic	**Control arm (N=xx)**	**Intervention arm (N=(xx)**
Sex		
Female	n (%)	n (%)
Male	n (%)	n (%)

Age; median (IQR)	xx (xx - xx)	xx (xx - xx)
BMI (kg / m^2)		
<25	n (%)	n (%)
≥ 25, < 30	n (%)	n (%)
≥ 30	n (%)	n (%)
Type of cancer		
Gynecological	n (%)	n (%)
Prostate	n (%)	n (%)
Cytostatic		
Before/during/after radiotherapy	n (%)	n (%)
Before and during radiotherapy	n (%)	n (%)
During and after radiotherapy	n (%)	n (%)
Radiation fractions		
Short	n (%)	n (%)
Long	n (%)	n (%)
Medicine dose		
Antidiarrheal agents	n (%)	n (%)
Bulking agents	n (%)	n (%)
Gas-reducing agents	n (%)	n (%)
Laxative agents	n (%)	n (%)
Smoking		
Never / stopped > 5 years ago	n (%)	n (%)
Smoked before RT / stopped < 5 years ago	n (%)	n (%)
Smoked before and during RT	n (%)	n (%)
Physically active		
No	n (%)	n (%)
Yes	n (%)	n (%)

5. ANALYSIS

5.1. Outcome definitions

5.1.1. Co-Primary outcomes

The co-primary outcome of change in concentration of hypersensitive CRP will be calculated as

CRP at four weeks after the end of radiotherapy – CRP at baseline

Hence, a positive value for the change will indicate an increase in CRP and a negative value will indicate a decrease.

The co-primary outcome of change in urgency syndrome will be calculated as

Urgency Syndrome at one-year after the end of radiotherapy – Urgency Syndrome at baseline

Higher scores of the Urgency Syndrome indicate worse symptoms. Hence a negative value for the change in Urgency score will indicate a worsening of symptoms over the duration of the trial, and a positive value will indicate an improvement in symptoms.

The Urgency Syndrome Score for each participant at each timepoint will be calculated using the factor loadings identified in Steineck et al [5].

All questions related to the urgency factor loadings in the paper by Steineck et al [5] are included in Fidura except one: 'Immediate need to defecate'. The reason is because it was very similar to the variable 'Sudden defecation urgency requiring lavatory'. The new question is on the same scale (1-7) as the old question, and we took the decision to substitute it without further amendments.

The urgency syndrome score for each participant and occasion is based on 14 questions, each of which is scored on a 1-7 scale, where 1 indicates the lowest level of symptoms and 7 the highest.

To calculate the score, first, for each participant and occasion, the variable will be standardized using the formula $X – \mu / \sigma$, where:

- X is the score for that participant for that specific question
- μ is the mean of that specific question from all participants (both arms) at the specific timepoint (baseline or follow-up)
- σ is the standard deviation of all responses (both arms) to that question at that timepoint

Then, each question will be multiplied by a loading factor. Finally, the scores will be summed up to a final score.

Q #	Question text (translated from Swedish)	Loading factor
46	Loose stools the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.71
47	Returned to the toilet within one hour after defecation to again empty the bowel the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.61

48	Sudden bowel movements that required an immediate visit to the toilet in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.85
49	Time to hold bowel movements during the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.69
50	Without warning leaked feces into the clothes, despite having previously emptied bowels, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.35
51	Without warning emptied all feces into the clothes in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.26
52	Leakage of loose stools, while awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.40
53	Leakage of loose stools, while asleep, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.22
57	Felt bloated for the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.32
58	Not been able to hold gas (farts) in the rectum when needed in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.25
60	Bad-smelling gas emissions (farts) that you have not been able to stop in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.27
67	Itching in the anus during the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.23
68	Pain in the anus during the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.22
69	Abdominal pain the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.34

5.1.2. Secondary outcomes

Unless otherwise stated, all secondary outcomes will be measured as change from baseline, as described above for the primary endpoints.

Leakage Syndrome

Leakage Syndrome scores will be calculated using the same method described above for Urgency Syndrome. The questions and associated factor loadings are described below:

Q	Question text (translated from Swedish)	Loading factor
50	Without warning leaked feces into the clothes, despite having previously emptied bowels, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.68
51	Without warning emptied all feces into the clothes in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.47
52	Leakage of loose stools, while awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.62
53	Leakage of loose stools, while asleep, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.53
54	Leakage of solid stools, while awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.43
55	Leakage of solid stools, while asleep, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.34
60	Smelled feces the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.52

Excessive Gas Discharge Syndrome

Excessive Gas Discharge Syndrome scores will be calculated using the same method described above for Urgency Syndrome. The questions and associated factor loadings are described below:

Q	Question text (translated from Swedish)	Loading factor
58	Not been able to hold gas (farts) in the rectum when needed in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.79

59	Audible passing of gas (farts) that you have not been able to stop in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.81
60	Bad-smelling gas emissions (farts) that you have not been able to stop in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.67

Excessive Mucus Discharge Syndrome

Excessive Mucus Discharge Syndrome scores will be calculated using the same method described above for Urgency Syndrome. The questions and associated factor loadings are described below:

Q	Question text (translated from Swedish)	Loading factor
64	Mucus from the intestine in the last three months at baseline the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.7
65	Mucus discharge from the rectum, when awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.81
66	Mucus discharge from the rectum, when asleep, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.51

Blood Discharge Syndrome

Blood Discharge Syndrome scores will be calculated using the same method described above for Urgency Syndrome. The questions and associated factor loadings are described below:

Q	Question text (translated from Swedish)	Loading factor
51	Without warning emptied all feces into the clothes in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.16
61	Blood from the intestine in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.53
62	Leakage of blood from the rectum, while awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.97

63	Leakage of blood from the rectum, while asleep, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.4
65	Mucus discharge from the rectum, when awake, in the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.18
67	Itching in the anus during the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.15
68	Pain in the anus during the last 3 months at baseline /the last week, 4 weeks after radiotherapy /the last three months, one-year after radiotherapy	0.14

5.2. Analysis methods

Primary outcome 1: CRP at four weeks

We will analyze the change in CRP using a linear regression model, with change in CRP as the outcome, and three covariates: randomized treatment (binary), site (binary) and baseline CRP (linear). No other covariate adjustment will be made.

Primary outcome 2: Urgency syndrome at one-year

We will analyze the change in Urgency syndrome using a linear regression model, with change in Urgency syndrome score as the outcome, and three covariates: randomized treatment (binary), site (binary) and baseline Urgency syndrome score (linear). No other covariate adjustment will be made.

Secondary outcomes

All other analyses of secondary outcomes will be analyzed using the same method as for the primary endpoints.

5.3. Statistical principles

We will not adjust for any covariates other than the treatment indicator, site, the baseline value of the outcome, unless there is a large difference between the two groups at baseline. For binary variables, a “large difference” is defined as greater than a 20-percentage point absolute difference in the proportions. For a continuous variable, a “large difference” is defined as one randomization group having a value more than 20% higher than the other group. The randomized groups will be compared and confounding variables with ≥ 20% difference between the groups will be included in the analysis.

We will visually assess the residuals for normality and homoscedasticity. If necessary, an equivalent non-parametric test will be performed.

5.4. Missing data

Missing data will not be imputed for the main analysis of primary and secondary outcomes. If there is an imbalance of missingness between the two randomized arms (defined as >20% difference between the missingness of an outcome between the arms), or if the overall missingness of an outcome variable is greater than 40% then we may perform multiple imputation as an exploratory analysis.

5.5. Additional analyses

We will repeat the above analyses on the per protocol population.

5.6. Harms

The present trail is a non-pharmacological clinical trial and no adverse events are expected. However, all adverse events during the study will be reported by trial arm.

5.7. Statistical software

Analysis will be performed in Stata or the programming language R.

5.8. References

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