Statistical analysis plan for clinical predictor analysis in the AIM-study

Statistical analysis plan (SAP) for:

Clinical predictors of effect of Antibiotic treatment in patients with chronic low back pain and Modic changes (the AIM study)

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This document is a supplement to the AIM-study protocol[1] and comprise a statistical analysis plan only for the article "Clinical predictors of effect of Antibiotic treatment in patients with chronic low back pain and Modic Changes (the AIM study)". Separate statistical analysis plans are made for other articles based on the AIM-study[2]. The current SAP is prepared in accordance with guidelines for Statistical analysis plans in clinical trials[3].

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List of Abbreviations and Definitions of Terms

Abbreviation or special term	Explanation
AIM	Antibiotics in Modic changes
CI	Confidence interval
ITT	Intention to treat
LBP	Low Back Pain
MCs	Modic changes
NRS	Numerical Rating Scale
ODI	Oswestry Disability Index
RMDQ	Roland Morris Disability Questionnaire
SAP	Statistical Analysis Plan
Study medication	Medication given in the study context containing either amoxicillin (test treatment) or placebo (the comparator)

Study objectives and outcomes

Main objective

To evaluate whether any subgroup of patients have a different treatment effect on RMDQ score at 1-year (12 months') follow-up.

Trial methods

The trial is a six centre, randomised, parallel-group, placebo-controlled trial. Treatment allocation is stratified on previous disc surgery with a 1:1:1:1 allocation and random block sizes of 4 and 6. Patients are randomised to either amoxicillin or placebo control.
The sample size was calculated to assess the treatment effect in the total sample as well as separately in each MC type group (I/II). In each MC type group, the study is designed to detect (β = 0.1, two-sided α = 0.05) a mean difference of 4 (SD 5) in the RMDQ score between the two treatment groups (amoxicillin or placebo) at one-year follow-up. See reference for further details of trial methods [1].

Final analysis for the clinical outcomes will take place after database locking, which will occur after all patients have finished their last visit and monitoring has been completed in all study centers (anticipated October 2018).

Statistical principles

All analyses described in this plan are considered *a priori* analyses in that they have been defined in the protocol and/or this SAP. All *post hoc* analyses will be identified as such in the article.

All relevant statistical tests will be 2-sided and the nominal p value will be reported. All confidence intervals presented will be 95% and 2-sided. The assumption of normal distribution will be checked by visual inspection of a QQ-plot. For skewed data the interquartile range will be reported.

All analyses will be carried out by a Ph.D-student using software package Stata version 15, and controlled by a senior statistician.

Hypotheses

We have predefined 4 primary subgroup analyses and 8 exploratory subgroup analyses. All subgroup analyses will be performed using ANCOVA on the ITT population with RMDQ at 1 year as dependent variable adjusted for baseline value of RMDQ and the stratification variables in the randomization (modic study group and former surgery for disc herniation) with an interaction term between subgroup variable and the treatment group.
In all subgroup analyses, the missing values of RMDQ will be substituted with the imputed values from the multiple imputation analysis as described in the Statistical analysis plan for the primary analysis[2].

For each subgroup analysis of a categorical variable, we will report the estimated effect of the treatment for all values of the subgroup variable. An estimated difference between the subgroups of more than 4 points on the RMDQ will be regarded as clinically relevant.

All subgroup analyses will be performed in a prioritized order according to table 1, reducing the problem of multiple testing. For all subgroup analyses we will keep a significance level (alpha) of 0.05 (two-sided) to claim statistical significance, as we regard these results hypothesis generating and want to avoid type II errors[4]. We will however, when interpreting the results, take into account that this significance level will induce a 46% chance of one or more false positive subgroup effects.

Results will be presented with a forest plot of effect estimates for each subgroup including confidence intervals, along with the test for the interaction between the subgroup and the treatment group. Each subgroup effect will be compared to the overall treatment effect (clearly marked with a bold line)[5].

Analysis populations

In the following definitions of terms, the study medication refers to the medication given as part of the study, and includes both amoxicillin and placebo. All subgroup analyses described in this SAP will be performed on the Intention-to-treat population, defined as all patients randomized to the study medication.

Trial population

The following summaries will be presented in a flow diagram:

The number of days recruiting, the number of patients screened, the number of patients included and randomised, the number of screened patients not included, and the reason for non-inclusion. The number of, if any, ineligible patients who were randomised will be reported, with reasons for

ineligibility. The flow diagram will also show separately lost to follow-up, withdrawal from follow-up and discontinuation of the intervention, all reported for each treatment arm and with timing and respective reasons.

Baseline patient characteristics

Patients will be described with respect to age, gender, BMI, smoking, educational level, comorbidity (Functional Comorbidity Index[6]), presence of leg pain, NRS-leg pain (0-10), subjective health complaints, emotional distress (Hopkins Symptom Check List-25), Fear-avoidance beliefs questionnaire (FABQ), symptom-specific well-being, duration of back pain, physically heavy work, compensated work injury or sick leave, level(s) with both Modic Change and previously herniated disc, and concomitant medication use, separately for the two treatment groups (see Table 2). Continuous variables will be summarized by mean and SD in case of normal distribution and median and interquartile range (difference between 75th and 25th quantiles) in case of skewed distribution. Categorical variables will be summarized by numbers and percentages. We will not perform any test of statistical significance, but rather note the clinical importance of any imbalance between the treatment groups.

Analyses

Table 1 – List of planned subgroup analyses

Table 1

Subgroup analysis	Motivation
Primary subgroup analyses	
1. Modic changes type	
Evaluate the influence of Modic type (Modic study group used as stratification variable as defined in the study protocol) on the effect of treatment group on the primary outcome. The hypothesis is a larger treatment effect in MC1 compared to MC2.	See Secondary objective (SO 1) in the protocol article[1]. Effect will be evaluated in each modic type (pre-defined hypothesis). In case of significant effect in each Modic type, or in case of only significant effect in just one Modic type, we want to know whether there is a significant difference in effect between the two Modic types.
2. Previous surgery on disc at the same level as Modic changes	
Evaluate the influence of previous surgery on disc (defined as surgery on the same level as the level of modic changes) on the effect of treatment group on the primary outcome. The hypothesis is a larger treatment effect in patients with previous disc surgery compared to those without. We will also evaluate the effect of treatment	Previous surgery is a possible cause of low-grade discitis. The Danish RCT was positive with a high number of patients with previous surgery[7], while a case series with few patients with previous surgery was negative[8]

group on the primary outcome separately for patients with previous surgery on disc and for patients without previous surgery on disc.	
3. Positive pain provocation test	
Evaluate the influence of positive pain provocation tests at baseline on the effect of treatment group on the primary outcome. Pain provocation tests include pain on lumbar flexion and extension in standing position and pain on palpation of lumbar vertebrae (Springer test), and will be assessed separately. The hypothesis is a larger treatment effect is patients with a positive Springer test compared to those with a negative Springer test.	See Key clinical supportive (KSOs) and exploratory objectives in the protocol article[1]. Springer test is borderline significant discriminator between patients with and without Modic[9]. Spinal tenderness may indicate regular spondylodiscitis[10]. Pain on extension is associated with MC type 1[11,12].
4. CRP	
Evaluate the influence of CRP in serum measured at baseline on the effect of treatment group on the primary outcome. CRP levels will be divided into 3 categories: <3, 3-10 and >10. An interaction term with this categorical variable and treatment group will be included in the analysis. The hypothesis is a larger treatment effect in those with higer CRP compared to those with CRP <3.	CRP in serum is associated with bacterial infection and inflammation.
Exploratory subgroup analyses	
1. Pain disturbs sleeping	
Evaluate the influence of disturbed sleeping due to pain, measured at baseline, on the effect of treatment group on the primary outcome. The hypothesis is a larger treatment effect in those patients with disturbed sleep due to pain compared to those without.	Night-time pain may indicate regular spondylodiscitis[10].
2. Constant pain at baseline	
Evaluate the influence of constant pain at baseline on the effect of treatment group on the primary outcome. The hypothesis is a larger treatment effect in those patients with constant pain compared to those with varying pain.	Constant pain may indicate regular spondylodiscitis[10].
3. Duration of back pain	
Evaluate the influence of duration of back pain symptoms on the effect of treatment group on the primary outcome. Duration will be categorized into 3 groups: <1 year, 1-2 years and >2 years. An interaction term with this categorical variable and treatment group will be included in the analysis. The hypothesis is a larger treatment effect in those with shorter duration of symptoms.	Recent disc prolapse could have increased perfusion in disc as part of disc repair, thereby increasing absorption of amoxicillin.
4. Age	

Evaluate the influence of age on the effect of treatment group on the primary outcome. Age will be categorized into 2 groups: ≤40 years and >40 years of age The hypothesis is a larger treatment effect in those with ≤40 years of age.	P.acne could be more prevalent in discs of young patients[13].
5. Sex	
Evaluate the influence of sex on the effect of treatment group on the primary outcome. The hypothesis is a larger treatment effect in men.	P.acne could be more prevalent in discs in men than in women[13].
6. NSAIDs	
Evaluate the influence of NSAIDs intake during treatment period on the effect of treatment group on the primary outcome. The hypothesis is a smaller treatment effect in those with NSAIDs intake during the treatment period.	Diclofenac could significantly reduce bioavailability of amoxicillin[14].
7. Compliance	
Evaluate the influence of noncompliance (see Adherence and Protocol Deviations in SAP for clinical outcomes (ref)) on the effect of treatment group on the primary outcome. The hypothesis is a lesser treatment effect in those with noncompliance.	Treatment effect could require a high degree of compliance, for obvious reasons.
8. Treatment effect at 3 months	
Evaluate the influence of treatment effect at 3 months on the effect of treatment group on the primary outcome. Treatment effect at 3 months will be defined as >30% reduction of RMDQ at 3 months compared to baseline value (dichotomous variable). The hypothesis is a larger treatment effect in those treatment effect at 3 months.	Treatment effect at 1-year could be predicted by treatment effect at 3 months.

Further analyses in case of clinically relevant and statistically significant differences in the subgroup analyses

In case of clinically relevant and statistically significant differences in a subgroup analysis, we will perform the same subgroup analyses with the Key supportive outcomes ODI and NRS Pain intensity. The purpose of these analyses will be to test if the interaction is consistent for these outcomes, as recommended in criteria to evaluate subgroup analyses[15].

In addition, if evidence of clinically relevant and statistically significant differences in two or more subgroup analyses, we will perform an analysis with all subgroup-treatment group interactions terms (both significant and non-significant in the previous analyses) to assess independency of any effect [15].

Other tables

Table 2 – Baseline Characteristics

	Amoxicillin (n =)	Placebo (n =)
Age		
Gender		
BMI		
Smoking- no. (%)		
Educational level		
Comorbidity		
Presence of leg pain		
NRS-leg pain, 0-10, mean (SD)		
Subjective health complaints ├		
Emotional distress, 1-4, mean (SD) •		
FABQ physical activity, 0-24, mean (SD) ►		
FABQ work, 0-42, mean (SD) ►		
Symptom specific well-being, 1-5, mean (SD) ¶		
Duration of back pain		
Physically heavy work (%)		
Compensated work injury or sick leave (%)		
Level of Modic Change and previous disc herniation - no. (%)		
L1/L2		
L2/L3		
L3/L4		
L4/L5		
L5/S1		
Concomitant medication use		
Analgesics for back pain – no.		
Opioids for back pain – no.		

• Emotional distress (Hopkins Symptom Checklist–25)
► Fear-avoidance beliefs Questionnaire
¶ Symptom specific well-being (5-point Likert scale)

Table 3 – Subgroup analyses for the primary outcome (RMDQ)- incomplete table

Variable	Amoxicillin (n =)		Placebo (n =)		Subgroup analysis	
	No of partici-pants	Overall mean (CI 95%)	No of partici-pants	Overall mean (CI 95%)	Interaction estimate	P-Value
Previous disc surgery	-	-	-	-		
Yes					-	-
No					-	-
Pain provocation test	-	-	-	-		
Pos					-	-
Neg					-	-
CRP	-	-	-	-		
<3					-	-
3-10					-	-
>10					-	-
Pain disturbs sleeping	-	-	-	-		
Yes					-	-
No					-	-
Constant pain	-	-	-	-		
Yes					-	-
No					-	-
Duration of back pain	-	-	-	-		
<1year					-	-
1-2 year					-	-
>2 years					-	-
Age	-	-	-	-		
<40					-	-
>40					-	-
Sex	-	-	-	-		
Female					-	-
Male					-	-
NSAIDs	-	-	-	-		
Yes					-	-
No					-	-

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