Achilles Tendinopathy Management

Statistical Analysis Plan

Achilles Tendinopathy Management (ATM): A multi-centre placebo controlled randomised controlled trial comparing Platelet Rich Plasma (PRP) to placebo (imitation) injection in adults with Achilles tendon pain.

ISRCTN Number:	ISRCTN13254422
Sponsor:	University of Warwick
Funding Body:	Arthritis Research UK
Ethics Approval date:	30th October 2015
Version Number:	1.0
Date:	16/05/2019
Stage:	Formal

Amendment No.	Date of Amendment	Date of Approval

WARWICK
CLINICAL TRIALS UNIT

Arthritis Research UK

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LIST OF ABBREVIATIONS/GLOSSARY

Abbreviation	Explanation
AE	Adverse Event
ATM	Achilles Tendinopathy Management
CI	Confidence interval
CONSORT	Consolidated Standards of Reporting Trials
EQ-5D-5L	EuroQol Five Dimensions questionnaire
DMC	Data Monitoring Committee
ITT	Intention To Treat
MAR	Missing At Random
MCAR	Missing Completely At Random
MICE	Multivariate Imputation by Chained Equations
MRI	Magnetic Resonance Imaging
NMAR	Not Missing At Random
PP	Per Protocol
PRP	Platelet Rich Rlasma
SAE	Serious Adverse Event
TSC	Trial Steering Committee
VAS	Visual Analogue Scale
VISA-A	Victorian Institute of Sports Assessment – Achilles questionnaire

SECTION 1: AIMS AND DESIGN OF THE TRIAL

1.1 Trial Design

Achilles Tendinopathy Management (ATM) Trial is a multi-centre, single blinded, randomised placebo controlled trial.

1.2 Objectives

1.2.1 Primary objective

The primary objective of this trial is to quantify and draw inferences on observed differences in the Victorian Institute of Sports Assessment – Achilles questionnaire (VISA-A) between the trial treatment groups at 6 months after randomisation.

1.2.2 Secondary objectives

The secondary objectives of the trial are

1. To quantify and draw inferences on observed differences in VISA-A status at 3 months after randomisation;
2. To identify any differences in health related quality of life between trial treatment groups at 3 and 6 months after randomisation;
3. To identify any differences in pain scores between trial treatment groups at 3 and 6 months after randomisation;
4. To determine the complication rate of platelet rich plasma (PRP) injections at 2 weeks, 3 and 6 months after randomisation.

1.3 Eligibility Criteria

1.3.1 Inclusion criteria

Patients will be eligible if all the criteria below are met:

- Aged 18 years or over;
- Pain at the mid-substance of the Achilles tendon for longer than three months;
- Ultrasound and/or MRI confirmation of tendinopathy.

1.3.2 Exclusion criteria

Patients will be ineligible if any of the following criteria are met:

- Presence of systemic conditions (including: diabetes, rheumatoid arthritis, peripheral vascular disease);
- Pregnant or actively trying to become pregnant, or breastfeeding at the time of randomisation;
- Have had prior Achilles tendon surgery or rupture on the index side;
- Previous major tendon or ankle injury or deformity to either lower leg;
- Have had a fracture of a long bone in either lower limb in the previous six months;
- Have any contraindication to receiving a PRP injection (haemodynamic instability, platelet dysfunction syndrome, cancer, septicaemia, systemic use of anticoagulant therapy (warfarin, dabigatran, heparin), local infection at site of the procedure);
- Are unable to adhere to trial procedures or complete questionnaires;
- Previous randomisation in the present trial;
- Previous PRP treatment into a tendon.

Patients presenting with bilateral Achilles tendinopathy will be randomised and treated as one unit i.e. the patient will be randomised rather than the tendon. However an index tendon will be identified (this will be the one the patient perceives to be more severe at the point of randomisation). These broad eligibility criteria will ensure that the results of this study can be readily generalised to the wider population.

1.4 Outcome Measures

1.4.1 Primary outcome

- VISA-A at 6 months

1.4.2 Secondary outcomes

- VISA-A at 3 months
- EQ-5D-5L at 3 and 6 months
- Visual analogue scale (VAS) for pain at 2 weeks, 3 and 6 months
- Complication rate of PRP injections at 2 weeks, 3 and 6 months

1.4.3 Safety

Adverse events (AE) and serious adverse events (SAE) will be reported.

SECTION 2: STRUCTURE OF THE STATISTICAL ANALYSIS PLAN

The remainder of the analysis plan has been divided into two main parts:

1. The monitoring of the trial;
2. The main statistical analysis.

SECTION 3: MONITORING OF THE TRIAL

Monitoring of the trial is a continual process, from the start to the end of the study. At the end of the trial following aspects will be assessed:

3.1 Recruitment of Patients

- The flow of patient recruitment will be summarised by centre and total in Table 1.
- Reasons for ineligibility will be summarised in Table 2 and will also be stated in the CONSORT diagram.
- Actual accrual will be continuously assessed against projected targets. A recruitment graph showing the number of patients recruited along the study by each centre and overall will be illustrated in Figure 1.
- A CONSORT diagram showing the flow chart of patients recruited in the study will be illustrated in Figure 2.

3.2 Randomisation

- Patient randomisation will be summarised in Table 3 by treatment arm in each centre and laterality strata to assess randomisation balance.
- Patient characteristics (age and sex) will also be summarised between randomised, ineligible and eligible but withholding consent (i.e. decline to participate) patients in Table 4 to assess characteristic differences between patient groups.

3.3 Sample Size

- The target sample size is 240, which provides 90% power to detect a mean difference of 12 in VISA-A score at 6 months between two treatment arms, assuming a standard deviation of 26, 5% type I error rate and approximately 15% loss to follow-up.
- The above is somewhat conservative, as it assumes that a simple unadjusted analysis will be used to compare group mean VISA-A scores at 6 months. In reality, the main study analysis will be adjusted by the baseline VISA-A score, which will be included as a covariate in the regression analysis. The pilot data suggested a significant positive association between baseline and 6 month VISA-A scores; Pearson correlation coefficient ≈ 0.6. Thus, assuming approximate normality for both baseline and 6 month VISA-A scores, and a correlation

coefficient of 0.6, the overall power of this study to detect a difference between group means of 12 increases to 98% in the adjusted analysis. Therefore, if the true difference between groups is smaller than anticipated we will still have good power to reject the null hypothesis. For instance, by simulating from the appropriate multivariate normal distributions, if the difference between groups were (i) 10 (effect size = 0.38), then the power would be 92%, (ii) 9 points (effect size = 0.35), then the power would be 86% and (iii) 8 points (effect size = 0.31), then the power would be 77%. Therefore, in summary, the proposed sample size gives us good power (~90%) for moderate effect sizes of the expected magnitude, and also reasonable power (~80%) for much smaller effect sizes.

3.4 Non-compliance (protocol violation and deviation)

The reasons for protocol deviations and violations will be tabulated by treatment arm in Table 5. At the beginning of the trial, the rate of non-compliance is considered as 100%, and as each non-compliant patient enters the trial through time, the rate of non-compliance will decrease.

3.5 Withdrawals

Withdrawals from the trial may occur after randomisation. Patients who decline to be contacted will be logged on the database from the point that they communicate their intention to the trial team and no further contact will be made. Data already collected will be retained and included in the analysis unless otherwise indicated. All withdrawals will be summarised by treatment arm in Table 6. Also all data up to the time of withdrawal will be used for the analysis (Intention to treat).

3.6 Follow-up of Patients

The follow-up rate is based on patients who complete the study questionnaires at, 2 weeks, 3 and 6 months after randomisation. The rate will be summarised by treatment arm in Table 1.

3.7 Safety Data

Treatment related adverse events and serious adverse events will be summarised in Table 7. However, the table may be integrated into Table 15 if the reporting is not complicated and all table numbers will be adjusted accordingly.

SECTION 4: STUDY DATA

4.1 Outcome Variables

OUTCOMES	TIME POINT	SCORING
Primary outcome		
VISA-A	At 6 months post randomisation	Summary of the total score (out of 100).
Secondary outcomes		
VISA-A	At 3 months post randomisation	Summary of the total score (out of 100).
EQ-5D-5L	At 3 months and 6 months post randomisation	Summary of each item given, the utility and VAS score (out of 100) summarised.
Pain VAS	At 2 weeks, 3 months and 6 months post randomisation	The VAS score (out of 100) will be summarised.
Complication rate	At 2 weeks, 3 months and 6 months post randomisation	Complication rate in each class will be summarised

4.2 Type of Populations

4.2.1 Intention to treat (ITT) population

The primary analysis will be performed on an Intention to treat (ITT) basis. That is to say that we will test whether PRP is better than placebo (i.e. an 'as-randomised analysis' or intention to treat (ITT) compares the outcomes of participants by assigned group). The ITT effect is the effect of treatment assignment rather than the effect of treatment taken (often called 'effectiveness' as opposed to 'efficacy'). A full 'Intention to treat' analysis is only possible when complete outcome data are available for all patients. One of the main reasons for advocating ITT analysis is that it gives an estimate as would be in the 'real world' and it also maintains the baseline comparability achieved by the randomisation process. If the initial random assignment is undermined, then confounding can be introduced and the internal validity of the results is consequently questionable.

4.2.2 Per protocol (PP) population

A per protocol (PP) anlaysis measures the effect of treatment in an "ideal" setting. A per protocol population includes the participants who followed the trial procedure and completed the allocated treatment. Hence, a per protocol analysis could introduce bias in the estimation of treatment effect.

Therefore, the PP population will be used to analyse primary outcome as part of the secondary analyses.

4.3 Analysis Datasets

4.3.1 Observed dataset

This will comprise of all the data observed (including follow-up) with missing values. For the VISA-A at baseline and 6 months, this dataset includes the patients with missing questionnaire item score no more than 20 points. The final score of these incomplete questionnaires will then be obtained by multiplying the total points of the completed items with the ratio of 100/(100-missing points), where 100 is the perfect score of the questionnaire.

4.3.2 Imputed dataset

Some participants may not provide complete data for VISA-A score at baseline or 6 months follow-up due to lack of completion of individual data items, voluntary withdrawal or general loss to follow up. The nature of missing data includes: (a) when it is not applicable (validly missing) and (b) it can be missing due to patient/health professional leaving fields blank when they should have completed the question with an answer (invalidly missing). The latter, when there are more than 20 missing points, will be examined for the different data mechanisms (MAR - missing at random; NMAR - not missing at random; MCAR - missing completely at random). The MICE (multivariate imputation by chained equations) method will be applied to impute VISA-A score at baseline and 6 months follow-up.

For the primary and secondary outcomes only the observed datasets will be used for the ITT analysis. Although missing data is not expected to be a problem for this study, the nature and pattern of the missingness will be carefully considered and imputation, where appropriate, will be made for completeness for VISA-A at baseline and 6 months follow-up.

The imputed dataset will be used for a sensitivity analysis for the primary outcome.

SECTION 5: MAIN STATISTICAL ANALYSIS

5.1 General Considerations

For patient characteristics data, continuous variables will be summarised using appropriate descriptive statistics, including n (number of non-missing cases), mean, standard deviation, median, range and nmiss (number of missing cases). Categorical variables will be summarised with frequency counts and percentages.

For outcome data, continuous variables will be summarised using appropriate descriptive statistics, including n, mean and 95% confidence interval (CI). Categorical variables will be summarised with frequency counts and percentages.

For the comparison of outcomes between treatment arms, t test will be used to test continuous outcomes and Pearson's chi-square test will be used to test categorical outcomes, unless otherwise stated. A two-sided p value <0.05 will be considered statistically significant.

The statistical analysis will be carried out using SAS. Data imputation, if necessary, will be conducted using STATA.

5.2 Descriptive Analysis of Baseline Characteristics and Blinding Success

Baseline patient characteristics will be summarised by treatment arm and in total (Table 8) and further stratified by centre and laterality (Table 9). Characteristics variables include age (continuous), height (continuous), weight (continuous), gender (binary), current smoker (binary), employment (nominal), socio-economic status (nominal), ethnicity (nominal) and treatment received for Achilles tendon pain (nominal).

Baseline VISA-A and EQ-5D-5L scores will be summarised by treatment arm in Tables 12 and 13, respectively.

Blinding success question is asked in the 6 months follow-up questionnaire. It will be summarised by treatment arm in Table 8.

5.3 Primary Analyses

5.3.1 VISA-A at 6 months follow-up

The primary analyses will be performed using the observed datasets on the basis of ITT population.

5.3.1.1 ITT analysis (observed dataset)

In the ITT analysis, mixed effect linear regression will be used to assess the difference in VISA-A score between treatment arms at 6 months follow-up, with the adjustment for design factors (centre and laterality), age, sex and baseline VISA-A score. Centre will be included in the model as a random effect, and age, sex, laterality and baseline VISA-A score as fixed effect. Adjusted treatment difference and 95% CI will be produced. Results will be presented in Table 10.

Residuals plots (residual vs fitted plot and residual Q-Q plot) will be used to assess the underlying model assumptions. These plots will be presented in Figures 3a and 3b, respectively.

If the above plots identify heteroscedasticity in model residuals, variance-stabilising transformation method, for example square root transformation and log transformation, will be considered to transform VISA-A score at 6 months follow-up. Model results of the transformed response data will be presented instead of those of the untransformed response data in Table 10.

5.4 Secondary Analyses

5.4.1 VISA-A at 6 months follow-up

The primary outcome will also be analysed using different analysis poluation, analytical method and dataset as part of the secondary analyses.

5.4.1.1 Per protocol analysis (observed dataset)

Mixed effect linear regression will be carried out with adjustment for covariates, as described in Section 5.3.1, on the basis of the PP population. The adjusted treatment effect and 95% CI will be presented in Table 11a. Residual plots will be presented in Figure 4a and 4b.

5.4.1.2 ITT analysis (observed dataset)

The primary outcome will be analysed without adjustment for covariates (unadjusted analysis) using the observed dataset and results will be summarised by treatment arm in Table 12.

5.4.1.3 ITT analysis (imputed dataset)

VISA-A at 6 months follow-up will be re-assessed using the imputed dataset on the basis of ITT population. Mixed effect linear regression will be carried out with adjustment for covariates, as described in Section 5.3.1. The adjusted treatment effect and 95% CI will be presented in Table 11b.

The following analyses of secondary outcomes will be performed using the observed dataset on the basis of ITT population.

5.4.2 VISA-A at 3 months follow-up

VISA-A score at 3 months follow-up will be summarised by treatment arm in Table 12. Analysis will also be adjusted for the covariates in the primary analysis.

5.4.3 EQ-5D-5L utility and VAS score at 3 and 6 months follow-up

EQ-5D-5L utility and VAS score at 3 and 6 months follow-up will be summarised by treatment arm in Table 13. Analysis will also be adjusted for the covariates in the primary analysis.

5.4.4 Pain VAS score at 2 weeks, 3 and 6 months follow-up

Pain VAS score at 2 weeks, 3 and 6 months follow-up will be summarised by treatment arm in Table 14. Analysis will also be adjusted for the covariates in the primary analysis.

5.4.5 Complication rates at 2 weeks, 3 and 6 months follow-up

Complication rate in each class at 2 weeks, 3 months and 6 months will be summarised by treatment arm in Table 15.

If it is felt there have been sufficient complications occurred in the trial, it may be useful to compare time to the development of each complication for each study participant. Kaplan Meier plot will be used to visualise the difference between treatment arms in Figure 5.

5.5 Non-compliance

If it is felt necessary to assess the pattern of non-compliance, risk of protocol violation will be compared between treatment arms to evaluate protocol adherence using logistic regression. Odds ratio and 95% CI will be tabulated in Table 16.

5.6 Sub-group Analyses

Pre-specified sub-group analyses will test the following variables for their interaction with treamtent arms:

- Single Achilles tendinopathy vs bilateral Achilles tendinopathy (defined by randomisation stratification): patients may have bilateral symptom when they meet the trial inclusion criteria. Some bilateral patients may be considered as having single Achilles tendinopathy when the non-trial Achillies tendon does not require surgical treatment. Therefore, these patients will be randomised and analysed as single Achilles tendinopathy.
- Short duration of symptom vs long duration of symptom: duration will be dichotomised using the value of median duration, which will be available at the time of final analysis.

The analyses will be performed on primary outcome only, in a mixed effect linear regression model on the basis of ITT population with adjustment for the same covariates used in the primary analyses as described in Section 5.3.1. Adjusted mean difference between treatment arms and 95% CI will be

presented as well as the p values for interaction (Table 17). The study sample size is not powered for the sub-group analyses.

5.7 Interim Analysis

No statistical stopping rules or interim analyses are planned.

SECTION 6: ADDITIONAL STATISTICAL ANALYSIS

No additional analyses are planned.

REFERENCES

APPENDIX A

Figure 1: Recruitment over time

Figure 2: CONSORT diagram for the ATM trial

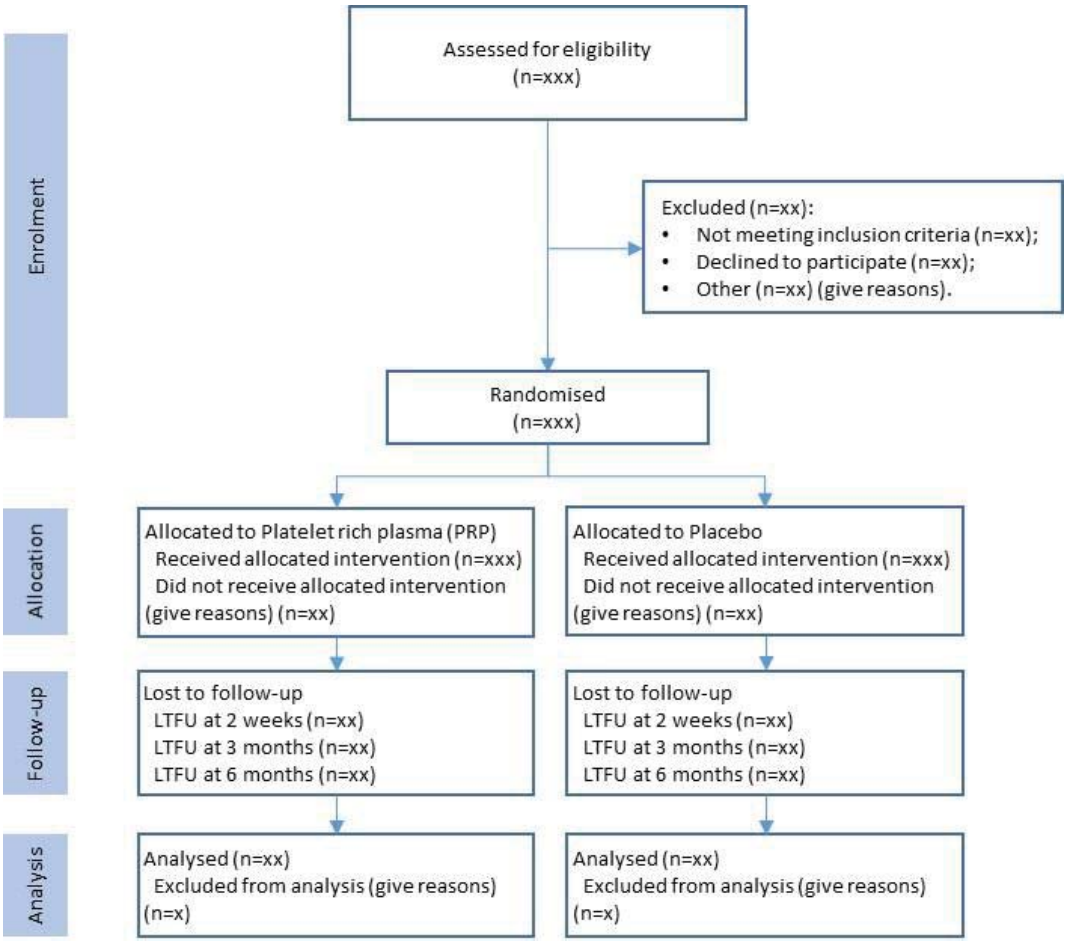

Figure 3a: Residuals versus fitted values of adjusted analysis of VISA-A score at 6 months follow-up (Intention to treat using observed dataset)

(Insert Figure 3a here)

Figure 3b: Residuals versus fitted values of adjusted analysis of VISA-A score at 6 months follow-up (Per protocol using observed dataset)

(Insert Figure 3b here)

Figure 4a: Residual normal Q-Q plot of adjusted analysis of VISA-A score at 6 months follow-up (Intention to treat using observed dataset)

(Insert Figure 4a here)

Figure 4b: Residual normal Q-Q plot of adjusted analysis of VISA-A score at 6 months follow-up (Per protocol using observed dataset)

(Insert Figure 4b here)

Figure 5: Kaplan Meier curve of time to complication (Intention to treat using observed dataset)

(Insert Figure 5 here)

APPENDIX B

I. Trial Monitoring

Table 1: Flow of patients in the ATM trial by centre and total

		Centre 1	Centre 2	Centre 3	…	Total
Screen to pre-randomisation	All patient screened	xx	xx	xx	xx	xx
	All eligible patients	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Excluded patients: patients meet exclusion criteria	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Eligible patients but withholding consent	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Randomisation	Patients randomised	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Randomised patients with baseline characteristics data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Randomised patients with baseline outcome data	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
2 weeks follow-up	Not due 2 weeks follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Follow-up complete	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Awaiting respond	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
3 months follow-up	Not due 3 months follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Follow-up complete	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Awaiting respond	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
6 months follow-up	Not due 6 months follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Follow-up complete	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Awaiting respond	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Lost to follow-up	At 2 weeks follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	At 3 months follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	At 6 months follow-up	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 2: Summary of ineligibility

		Total
Ineligibility	Reason 1	xx
	Reason 2	xx
	Reason 3	xx
	…	xx
	Total	xx

Table 3: Summarised randomisation in each treatment arm by centre and laterality strata

Centre	Laterality	Treatment	
		Placebo	PRP
Centre 1	Single	xx (xx.x%)	xx (xx.x%)
	Bilateral	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)
Centre 2	Single	xx (xx.x%)	xx (xx.x%)
	Bilateral	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)
Centre 3	Single	xx (xx.x%)	xx (xx.x%)
	Bilateral	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)
…	Single	xx (xx.x%)	xx (xx.x%)
	Bilateral	xx (xx.x%)	xx (xx.x%)
	Total	xx (xx.x%)	xx (xx.x%)

Table 4: Patient characteristics (randomised vs not randomised)

		Randomised patients	Ineligible patients	Eligible but withholding consent patients
Age (year)	N	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x

	Median	xx.x	xx.x	xx.x
	Minimum	xx.x	xx.x	xx.x
	Maximum	xx.x	xx.x	xx.x
	Missing	xx	xx	xx
Gender	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 5: Non-compliance by treatment arm and total

		Placebo	PRP	Total
Deviations	Reason 1	xx (xx.x%)	xx (xx.x%)	xx
	Reason 2	xx (xx.x%)	xx (xx.x%)	xx
	Reason 3	xx (xx.x%)	xx (xx.x%)	xx
	…	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx
Violations	Reason 1	xx (xx.x%)	xx (xx.x%)	xx
	Reason 2	xx (xx.x%)	xx (xx.x%)	xx
	Reason 3	xx (xx.x%)	xx (xx.x%)	xx
	…	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx

Table 6: Withdrawal at each follow-up by treatment arm and total

	Time point	Placebo	PRP	Total
Withdrawal	After randomisation but before 2 weeks follow-up	xx (xx.x%)	xx (xx.x%)	xx
	After 2 weeks follow-up but before 3 months follow-up	xx (xx.x%)	xx (xx.x%)	xx

	After 3 months follow-up but before 6 months follow-up	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx

Table 7: Adverse events and serious adverse events by treatment arm and total

		Placebo	PRP	Total
Adverse events	Reason 1	xx (xx.x%)	xx (xx.x%)	xx
	Reason 2	xx (xx.x%)	xx (xx.x%)	xx
	…	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx
Serious adverse events	Reason 1	xx (xx.x%)	xx (xx.x%)	xx
	Reason 2	xx (xx.x%)	xx (xx.x%)	xx
	…	xx (xx.x%)	xx (xx.x%)	xx
	Total	xx (xx.x%)	xx (xx.x%)	xx

II. Baseline Characteristics and Measures

Table 8: Baseline patient characteristics by treatment arm and total

		Placebo	PRP	Total
Age (year)	N	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Missing	xx	xx	xx
Gender	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Height (cm)	N	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x

	Missing	xx	xx	xx
Weight (kg)	N	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Missing	xx	xx	xx
Current smoker	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Employment	Full-time employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Part-time employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Self-employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Retired/inactive	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unpaid work	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unemployed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Full time student	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Carer	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Socio-economic status	Unskilled manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Skilled manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unskilled non-manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Skilled non-manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Professional	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity	White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Asian/Asian British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Black/African/Caribbean /Black British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mixed/Multiple ethnic groups	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Treatment received: Injections	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Physiotherapy	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Surgery	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Acupuncture	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Podiatry	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Prescribed insoles	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x

		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Treatment received: Other	No		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Yes		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Session number	N	xxxx	xxxx	xxxx
		Mean	xx.x	xx.x	xx.x
		Std. Deviation	xx.x	xx.x	xx.x
		Median	xx.x	xx.x	xx.x
		Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Blinding success	I think I had the autologous platelet rich plasma injection		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	I think I had the placebo imitation injection		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	I am not sure what treatment I received		xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Table 9: Baseline patient characteristics by centre and laterality

		Centre 1				Centre 2				…			
		Single		Bilateral		Single		Bilateral		Single		Bilateral	
		Placebo	PRP	Placebo	PRP	Placebo	PRP	Placebo	PRP	Placebo	PRP	Placebo	PRP
Age (year)	N	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Missing	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Gender	Male	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Female	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Height (cm)	N	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Missing	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Weight (kg)	N	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx	xxxx
	Mean	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Std. Deviation	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x

	Median	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x	xx.x
	Range	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
	Missing	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx	xx
Current smoker	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Employment	Full-time employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Part-time employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Self-employed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Retired/inactive	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unpaid work	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unemployed	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Full time student	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Carer	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Socio-economic status	Unskilled manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Skilled manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

	Unskilled non-manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Skilled non-manual	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Professional	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Ethnicity	White	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Asian/Asian British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Black/African/Caribbean/Black British	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Mixed/Multiple ethnic groups	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Other	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

III. Primary Analyses

Table 10: Adjusted treatment difference of VISA-A score at 6 months follow-up with 95% confidence interval (Intention to treat using observed dataset)

	Placebo		PRP		Difference (PRP-Placebo)		p value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	
VISA-A at 6 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	0.xxx

IV. Secondary Analyses

Table 11a: Adjusted treatment difference of VISA-A score at 6 months follow-up with 95% confidence interval (Per protocol using observed dataset)

	Placebo		PRP		Difference (PRP-Placebo)		p value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	
VISA-A at 6 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	0.xxx

Table 11b: Adjusted mean VISA-A score at 6 months follow-up with 95% confidence interval by treatment arm (imputed dataset)

	Placebo		PRP		Difference (PRP-Placebo)		p value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	
VISA-A at 6 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	0.xxx

Table 12: Summary statistics for VISA-A score at baseline, 3 and 6 months follow-up by treatment arm and total

	Placebo		PRP		Total		Unadjusted difference (PRP-Placebo)		p value	Adjusted difference (PRP-Placebo)		p value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)		N	Mean (95% CI)	
VISA-A at baseline	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)			NA			NA
VISA-A at 3 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx
VISA-A at 6 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx			

Note: NA: Not applicable.

Table 13: Summary statistics for EQ-5D-5L at baseline, 3 and 6 months follow-up by treatment arm and total

Time point	Item	Placebo		PRP		Total		Unadjusted difference (PRP-Placebo)		p value	Adjusted difference (PRP-Placebo)		p value
		N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)		N	Mean (95% CI)	
Baseline	Mobility	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Self-care	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Usual activities	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						

	Pain/discomfort	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Anxiety	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	EQ-5D-5L utility score	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)						
	EQ-5D-5L VAS	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)						
3 months follow-up	Mobility	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Self-care	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Usual activities	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Pain/discomfort	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Anxiety	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	EQ-5D-5L utility score	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx
	EQ-5D-5L VAS	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx
	Mobility	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						

6 months follow-up	Self-care	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Usual activities	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Pain/discomfort	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	Anxiety	xxxx	xx.x%	xxxx	xx.x%	xxxx	xx.x%						
	EQ-5D-5L utility score	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx
	EQ-5D-5L VAS	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx

Note: NA: Not applicable.

Table 14: Summary statistics for pain VAS at 2 weeks, 3 and 6 months follow-up by treatment arm and total

	Placebo		PRP		Total		Unadjusted difference (PRP-Placebo)		p value	Adjusted difference (PRP-Placebo)		p value
	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)	N	Mean (95% CI)		N	Mean (95% CI)	
Pain VAS at 2 weeks follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)						0.xxx

Pain VAS at 3 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx
Pain VAS at 6 months follow-up	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	xxxx	xx.x (xx.x, xx.x)	x	xx.x (xx.x, xx.x)	0.xxx	x	xx.x (xx.x, xx.x)	0.xxx

Table 15: Frequency and percentage of complication rate at 2 weeks, 3 and 6 months follow-up by treatment arm and total

Complication class		Placebo	PRP	Total	p value
Bruising and discomfort at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Fainting at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Infection at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Mild discomfort and bleeding at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Swelling at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Skin discolouration at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Allergic reaction at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Other at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Total at 2 weeks	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	

	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Bruising and discomfort at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Fainting at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Infection at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Mild discomfort and bleeding at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Swelling at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Skin discolouration at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Allergic reaction at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Other at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Total at 3 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	

Bruising and discomfort at 6 months	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Fainting at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Infection at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Mild discomfort and bleeding at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Swelling at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Skin discolouration at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Allergic reaction at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Other at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
Total at 6 months	Yes	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	0.xxx
	No	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Unknown	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	
	Missing	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	

Table 16: Estimated odds ratio of non-compliance

	Placebo	PRP	Odds ratio	95% CI	p value
Non-compliance	XX (XX.X%)	XX (XX.X%)	xx.x	(xx.x, xx.x)	0.xxx

Table 17: Adjusted treatment difference of VISA-A score at 6 months according to sub-group characteristics

	N (PRP/Placebo)	Mean treatment difference (95% CI) (PRP-Placebo)	p for interaction
Laterility			
Single	Xxxx/xxxx	xx.x (xx.x, xx.x)	0.xxx
Bilateral	Xxxx/xxxx	xx.x (xx.x, xx.x)	
Duration of symptom			
<= median duration	Xxxx/xxxx	xx.x (xx.x, xx.x)	0.xxx
> median duration	Xxxx/xxxx	xx.x (xx.x, xx.x)	