Statistical Analysis Plan

Orthodontic Patient Experience of Intraoral Scanners Versus Alginate Impressions in the UK: a Single-Centre Randomised Controlled Crossover Trial

SHORT TITLE/ ACRONYM OPESI Trial

	Name	Signature	Date *(DD/MMM/YYYY)*
Study Statistician	J Beckhelling	Jacqueline Beckhelling	Digitally signed by Jacqueline Beckhelling Date: 2022.11.09 14:55:54 Z
Chief Investigator	Alison Murray		09/11/2022

Protocol Version Number and Date	V2.0 20/02/2022	**IRAS reference**	307434

Version Number	Date	Author	Description of Changes
V1.0	8th Nov 2022	J Beckhelling	

Guidance for using this template:

All black text could be kept for the finalised version of any SAP.

All blue text is guidance to be referred to throughout the development of the SAP and deleted before finalising.

All red text is correct when referencing the CTIMP protocol template (CTU/TEM/020 – v2.0 – 14/Sep/2017), but is likely to need updating the section numbering for each individual study's protocol.

The numbering of each section should match that of the dummy tables, that way enabling any individual item to be tracked from the SAP, through the do file and into the analysis results. Numbering referencing section in the study protocol should also be given to enable tracking details previous to the SAP.

Derby Clinical Trials Support Unit

TABLE OF CONTENTS

[A] SAMPLE SIZE 3
[A.1] Sample Size Estimation / Power Calculation [Protocol Sec. 10.1] 3
[A.2] Sample Size Amendments After Interim Analysis 3
[A.3] Final Sample Size 3

[B] RANDOMISATION [PROTOCOL SEC. 7.3] 3

[C] INTERIM ANALYSIS [PROTOCOL SEC. 10.6] 3

[D] JUSTIFICATION FOR INTERIM ANALYSIS 3
[D.1] Definition of Endpoints used in Interim Analysis 3
[D.2] Statistical Methods for Interim Analysis 3

[E] FINAL STATISTICAL ANALYSIS [PROTOCOL SEC. 10.3] 3
[E.1] Summary of Baseline Data [Protocol Sec. 10.3.1] 3
[E.2] Definition of Primary Endpoint [Protocol Sec. 10.3.2] 4
[E.3] Statistical Methods for Primary Analysis [Protocol Sec. 10.3.2] 4
[E.4] Definition of Secondary Endpoints [Protocol Sec. 10.3.2] 4
[E.5] Statistical Methods for Secondary Analyses [Protocol Sec. 10.3.2] 5
[E.6] Statistical Methods for Sub-group Analyses [Protocol Sec. 10.4] 5
[E.7] Statistical Methods for Sensitivity Analyses [Protocol Sec. 10.3.2] 5
[E.8] Definition of Safety Endpoints [Protocol Sec. 8] 5
[E.9] Statistical Methods for Safety Endpoints 5

[F] ANALYSIS GROUPS AND MISSING DATA 5
[F.1] Definition of Analysis Groups [Protocol Sec. 10.7] 5
[F.2] Definition of Inclusion Groups 6
[F.3] Procedure for Accounting for Missing, Unused, and Spurious Data [Protocol Sec. 10.8] 6

[G] COMMENTS 6

APPENDIX A. DUMMY TABLES 7

APPENDIX B. CONSORT DIAGRAM 9

[A] Sample Size

[A.1] Sample Size Estimation / Power Calculation [Protocol Sec. 10.1]

[A.1.1] The sample size calculations are recorded in "Dentalscans Sample Size Verification_v1 25Jun2021.pdf" in the eTMF and summarised in the protocol.

[A.2] Sample Size Amendments After Interim Analysis

[A.2.1] Not applicable – there will be no interim analysis

[A.3] Final Sample Size

[A.3.1] Not applicable

[B] Randomisation [Protocol Sec. 7.3]

[B.1.1] Full details of the randomisation are recorded in the randomisation specification "OPESI Randomisation Specification_TRUNCATED_v1.0_13APR2022" in the eTMF and summarised in the protocol.

[C] Interim Analysis [Protocol Sec. 10.6]

[C.1.1] There will be no interim analyses.

[D] Justification for Interim Analysis

[D.1] Definition of Endpoints used in Interim Analysis

[D.1.1] Not applicable

[D.2] Statistical Methods for Interim Analysis

[D.2.1] Not applicable

[E] Final Statistical Analysis [Protocol Sec. 10.3]

[E.1] Summary of Baseline Data [Protocol Sec. 10.3.1]

[E.1.1] Descriptive statistics will be presented to summarise the distribution of baseline variables (age and gender) across each of the randomisation groups. Age will be reported with means & 95% confidence intervals (95% CI), if shown to be normally distributed, using a combined skewness and kurtosis test, otherwise will be reported with medians & Interquartile Ranges (IQR). Gender will be reported with frequencies & percentages.

[E.1.2] A Consolidated Standards of Reporting Trials (CONSORT) flow diagram will be produced, showing the frequency of patients / participants;

- Assessed for eligibility (screening),
- Found eligible,
- Reasons for not consenting,
- Given consent,
- Excluded before randomisation (and the frequency of each reason for withdrawing consent),
- Randomised,
- Allocated to each randomisation group,
- That received each allocated intervention,

- That did not receive each allocated intervention,
- Lost to follow-up (and the frequency of each reason for loss to follow-up) for each randomisation group,
- Analysed for each randomisation group,
- Not analysed (and the frequency of each reason for not being analysed) for each randomisation group.

[E.2] Definition of Primary Endpoint [Protocol Sec. 10.3.2]

[E.2.1] The primary endpoint is the difference between two (identical) visual analogue scales (VAS), both completed by the patient, measuring the comfort of each procedure. One VAS will measure the comfort of the impression and the other VAS will measure the comfort of the scan. Each VAS will be measured by two operators and a mean of their measurements will be recorded for each scale. The difference between each participant's mean comfort VAS scores for the two procedures will be calculated.

[E.3] Statistical Methods for Primary Analysis [Protocol Sec. 10.3.2]

[E.3.1] The mean of the differences between procedures will be reported for each treatment sequence with 95% confidence intervals. The difference between the paired VAS will be compared using analysis of variance (ANOVA) that will analyse the period, treatment and sequence effects of the comfort scores. Analysis of the primary endpoint will be assessed using 2-sided tests with a significance level of 0.05.

[E.4] Definition of Secondary Endpoints [Protocol Sec. 10.3.2]

[E.4.1] Patients will complete 4 secondary endpoints, each of which will be measured using two (identical) VAS, both completed by the patient, to measure four different features of each procedure (see section E.4.2 for details of the features the patients will assess). For each assessment, a VAS will be scored for the impression and another for the scan. Each VAS will be measured by two operators and a mean of their measurements will be recorded for each VAS.

[E.4.2] The patients will assess

1. pain
2. the speed of the procedure,
3. nausea and / or coughing
4. to what degree the patient would recommend the procedure

[E.4.3] Orthodontic operators will complete 4 secondary endpoints, each of which will be measured using two (identical) VAS, both completed by the operator, to measure four different features of each procedure (see section E.4.4 for details of the features the operators will assess). For each assessment, one VAS will be a measurement of the impression and the other will measure the scan. Each completed VAS will be measured by two operators (using rulers) and a mean of their measurements will be recorded for each scale.

[E.4.4] The operators will assess

1. Ease of impression
2. Confidence taking the impression
3. Relative speed of the impression
4. whether the patient felt sick or coughed during the procedure

[E.4.5] The time taken to make the impression or complete the scan will be recorded (mins)

[E.4.6] A secondary analysis of the primary outcome will be undertaken using a two-period two-treatment mixed effects model.

[E.4.7] If some participants have not complied with the protocol, a second analysis of the primary outcome will be conducted just including participants that were compliant.

[E.5] Statistical Methods for Secondary Analyses [Protocol Sec. 10.3.2]

[E.5.1] Eight of the secondary outcomes will be recoded using VAS scores (see Sections E.4.2 and E.4.4). The differences between the paired VAS scores of these secondary outcomes will reported using means and 95% confidence intervals. They will be compared using analysis of variance (ANOVA) that will analyse the period, treatment and sequence effects of the comfort scores. Analysis of the secondary endpoint will be assessed using 2-sided tests with a significance level of 0.05.

[E.5.2] The mean difference in the time required for each procedure (Section E.4.5) will be reported, with 95% confidence intervals. The difference in time will be compared using analysis of variance (ANOVA) that will analyse the period, treatment and sequence effects of the comfort scores. Analysis of the secondary endpoint will be assessed using 2-sided tests with a significance level of 0.05.

[E.5.3] The operator's preference for each impression (Section E.4.6) will be tabulated and reported using frequencies and percentages.

[E.5.4] The secondary analysis of the primary outcome using a two-period two-treatment mixed effects model (Section %.4.7) will be undertaken with participant effects treated as random and a treatment-by-period interaction (for this analysis, the carryover effect) included in the model. The mean effects will be reported, with 95% confidence intervals.

[E.5.5] The potential second analysis of the primary outcome (Section E.4.8) will be a per protocol analysis of the difference between the paired VAS. This will be carried out using an analysis of variance (ANOVA) that will analyse the period, treatment and sequence effects of the comfort scores. Analysis of the primary endpoint will be assessed using 2-sided tests with a significance level of 0.05. The mean effects of this model will be reported, with 95% confidence interval

[E.6] Statistical Methods for Sub-group Analyses [Protocol Sec. 10.4]

[E.6.1] There will be no sub-group analyses

[E.7] Statistical Methods for Sensitivity Analyses [Protocol Sec. 10.3.2]

[E.7.1] If there are missing data in the primary endpoint, the plausibility that outcome data are missing at random (MAR) from the primary endpoint will be examined, and if it doesn't hold, sensitivity analysis will be conducted. Otherwise, sensitivity analyses will not be undertaken.

[E.8] Definition of Safety Endpoints [Protocol Sec. 8]

[E.8.1] The safety endpoints will be the reported SAEs and SUSARs.

[E.9] Statistical Methods for Safety Endpoints

[E.9.1] The number and percentage of patients reporting a SAE or SUSAR will be summarised by treatment group and compared using a Chi-Square test.

[F] Analysis Groups and Missing Data

[F.1] Definition of Analysis Groups [Protocol Sec. 10.7]

[F.1.1] Modified Per Protocol: All participants who were randomised and experienced at least one of the study treatments will be included in the primary analysis. Participants will be

analysed according to the treatment sequence they received, if this differs from the treatment sequence to which they were allocated.

The safety data will be reported for all participants who experienced at least one of the study treatments. They will be reported according to the treatment they received at the time of experiencing the SAE or SUSAR, or the most recent treatment if the event occurred after the method was administered.

[F.1.2] Per protocol: If required, the secondary analysis will be carried out on patients who experienced both procedures. They will be analysed according to the treatment sequence they received if this differs from the treatment sequence to which they were allocated.

[F.2] Definition of Inclusion Groups

[F.2.1] Complete Dataset Population: Missing data are expected to be small and the primary analysis is planned to be carried out on a complete case basis. For the secondary analyses, any participant who has incomplete data will be excluded from the analysis that requires those data.

[F.3] Procedure for Accounting for Missing, Unused, and Spurious Data [Protocol Sec. 10.8]

[F.3.1] If there are missing data in the primary endpoint, then multiple imputation using chained equations will be applied. Missing data will not be imputed for any of the secondary endpoints, which will be analysed on a complete case basis.

[G] Comments

[G.1.1] The analyses will be carried out using STATA.

[G.1.2] The protocol describes another secondary outcome, which is the operator's preference for scans or impressions. This will be analysed qualitatively and is therefore outside the scope of this analysis plan.

Appendix A. Dummy Tables

SAP section ref	PRIMARY ANALYSIS	Treatment X (n=*N*)	Treatment Y (n=*N*)	Difference between treatments	p-value
D.3.1	**Primary Continuous Endpoint (unit)** *mean (95% CI) or median (IQR)*	*X (X to X)*	*X (X to X)*	*X (X to X)*	*X*

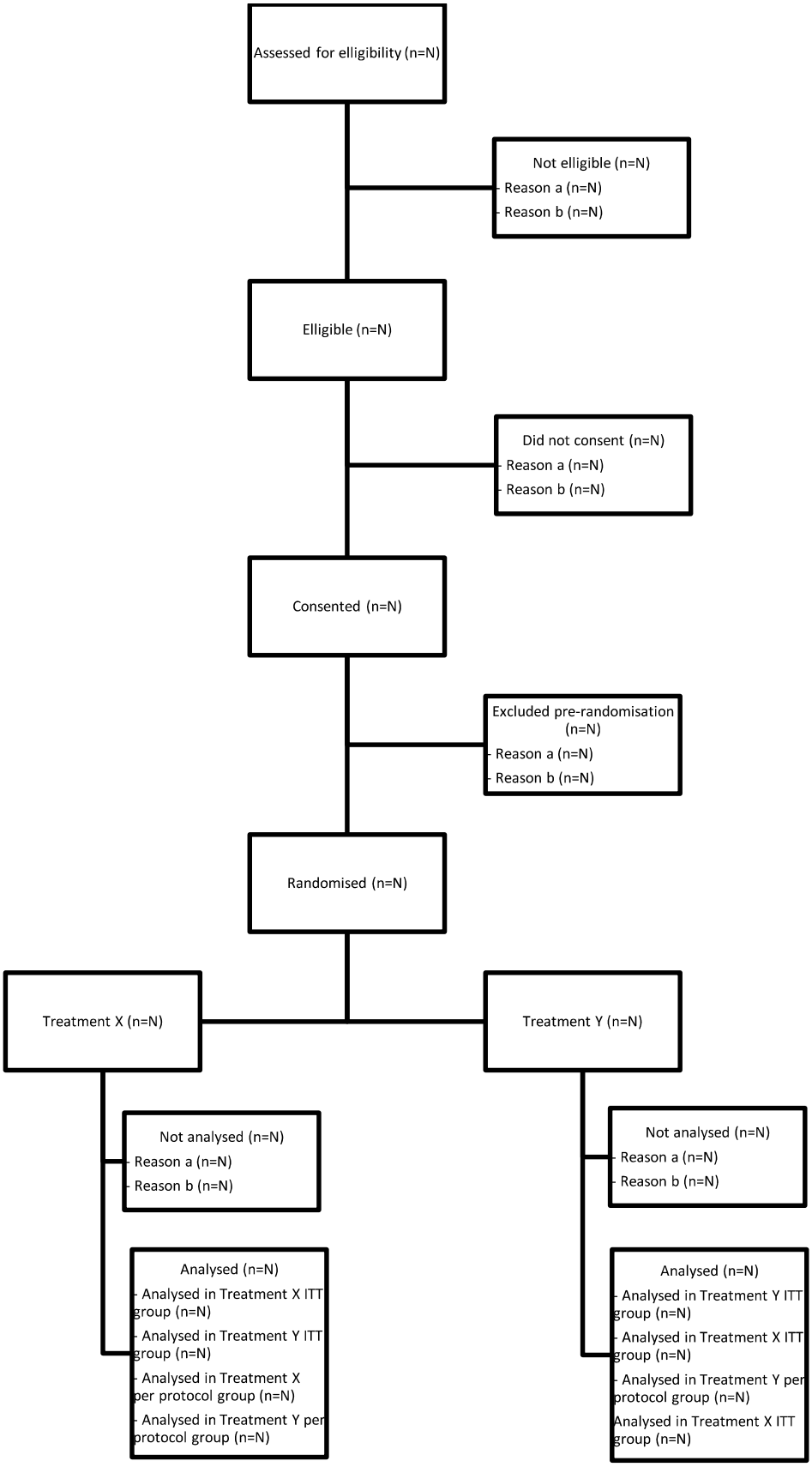
SAP section ref	PRIMARY ANALYSIS	Treatment X (n=*N*)	Treatment Y (n=*N*)	Difference in proportions between treatments	Relative Ratio / Odds Ratio	p-value
D.3.1	**Primary Categorical Endpoint (unit)** *n (%)*	*n (%)*	*n (%)*	*X (X to X)*	*X (X to X)*	*X*

SAP section ref	SUMMARY OF BASELINE DATA	Treatment X (n=*N*)	Treatment Y (n=*N*)
D.1.1	**Continuous Endpoint (unit)** *mean (95% CI) or median (IQR)*	*X (X to X)*	*X (X to X)*
D.1.1	**Categorical Endpoint** *n (%)*	-	-
	Category 1	*X (X)*	*X (X)*
	Category 2	*X (X)*	*X (X)*
	Category 3	*X (X)*	*X (X)*

SAP section ref	SAFETY ENDPOINTS	Study Population (n=*N*)
D.9.1	**AR diagnosis** *n (%)*	-
	Diagnosis A	*X (X)*
	Diagnosis B	*X (X)*

SAP section ref	SAFETY ENDPOINTS	Treatment X (n=*N*)	Treatment Y (n=*N*)	Difference between treatments	p-value
D.9.2	**Number of SARs** *mean (95% CI) or median (IQR)*	*X (X to X)*	*X (X to X)*	*X (X to X)*	*X*
D.9.3	**Number of SAEs** *mean (95% CI) or median (IQR)*	*X (X to X)*	*X (X to X)*	*X (X to X)*	*X*

Appendix B. CONSORT Diagram



SAP section D.3.2