National Institute for Health Research

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Femto Assisted FACT Cataract Trial

A Randomised, Single Masked, Non-inferiority Trial of Femtosecond Laser Assisted vs Manual Phacoemulsification Cataract Surgery for Adults with Visually Significant Cataract: the FACT trial

UCL CCTU ID:	**CTU/2012/046**
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STATISTICAL ANALYSIS PLAN (SAP)

VERSION 2.0, 09 DEC 2018

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2. ABBREVIATIONS

Acronyms	Meaning
CCTU	Comprehensive Clinical Trials Unit
CDVA	Corrected Distance Visual Acuity
CF	Counting Fingers
CI	Confidence Interval
CRF	Case Report Form
eSMF	electronic Statistical Master File (stored electronically)
Femto	Femtosecond laser-assisted phacoemulsification
HM	Hand Movements
IQR	Interquartile Range
MAR	Missing at Random
MICE	Multiple Imputation by Chained Equations
NPL	No Perception of Light
OR	Odds ratio
Phaco	Standard phacoemulsification
PL	Perception of Light
REML	REstricted Maximum Likelihood
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SER	Spherical Equivalent Refraction
TMF	Trial Master File
TSC	Trial Steering Committee
UDVA	Unaided Distance Visual Acuity
VA	Visual Acuity
VAS	Visual Analogue Scale

3. ABSTRACT – BACKGROUND AND DESIGN

Aim and objectives: The aim of this study is to assess the clinical effectiveness and cost-effectiveness of laser assisted cataract surgery in NHS cataract surgical units.

The primary objective is to demonstrate that Femtosecond laser-assisted cataract surgery (Femto) is not inferior to standard Phacoemulsification (Phaco), by assessing Unaided Distance Visual Acuity (UDVA, logMAR) in the study eye 3 months after surgery using a standard ETDRS chart at a starting distance of 4 metres.

Population studied: 808 patients with visually symptomatic cataract(s).

Trial design: FACT is a pragmatic two arm randomised controlled non-inferiority trial, with an accompanying economic analysis. Patients will be randomly allocated to either Femto or Phaco on the day of surgery. Each patient will have a 3 and 12 months trial visit and will also complete trial questionnaires that will be posted to them at 6 weeks and 6 months.

Sample size: Assuming a non-inferiority limit of 0.1logMAR, using a one-sided 2.5% significance level and 90% power it is calculated that 344 patients per group are required for the study, adjusting for clustering of patients within surgeons. Allowing for a 15% drop-out rate, it is anticipated that a total of 808 patients will need to be randomised.

Randomisation: Patients will be equally randomised to either surgical procedure using minimisation with a random element, with surgeon, whether in the local clinician's opinion the patient will require surgery on one or both eyes, and treatment centre as stratification factors.

Unit of analysis: The study eye is defined as the first eye to undergo cataract surgery and is chosen by the patient in discussion with the surgeon. For patients having surgery on both eyes, the fellow eye will also receive the allocated intervention unless the patient expresses a wish not to receive the same intervention.

Masking: Patients and centre staff will not be masked to the treatment allocation due to the nature of the intervention. The optometrist assessing visual acuity will be masked to the trial intervention.

4. OUTCOME MEASURES

4.1 Primary outcome

The primary outcome measure is UDVA logMAR at 3 months following surgery in the study eye measured using a standard ETDRS chart at a starting distance of 4 metres.

4.2 Secondary outcomes

a) Effectiveness

1. UDVA, logMAR at 12 months following surgery in the study eye using the ETDRS chart at a starting distance of 4 metres.

   The remaining secondary effectiveness outcomes listed below will be measured at both 3 and 12 months following surgery in the study eye. Please note that fellow eye

refers to fellow eyes eligible for trial surgery that received surgery after the study eye and within 3 months of study eye surgery.

2. UDVA, logMAR in the fellow eye using the ETDRS chart at a starting distance of 4 metres.
3. UDVA, logMAR with both eyes using the ETDRS chart at a starting distance of 4 metres.
4. Corrected distance visual acuity (CDVA, logMAR) in the study eye using the ETDRS chart at a starting distance of 4 metres.
5. CDVA, logMAR in the fellow eye using the ETDRS chart at a starting distance of 4 metres.
6. CDVA, logMAR with both eyes open using the ETDRS chart at a starting distance of 4 metres.
7. Percentage of patients within ±0.5 and within ±1.0 dioptre of intended refractive outcome in the study eye.
8. Percentage of patients within ±0.5 and within ±1.0 dioptre of intended refractive outcome in the fellow eye.

b) Safety at 3 and 12 months following surgery in the study eye:

1. Frequency of intra-operative events (e.g. posterior capsule tears, dropped lens) in the study eye.
2. Frequency of intra-operative events (e.g. posterior capsule tears, dropped lens) in the fellow eye.
3. Frequency of Adverse Events (e.g. retinal tear or retinal detachment, macular oedema) and Serious Adverse Events (SAEs) in the study eye.
4. Frequency of Adverse Events (e.g. retinal tear or retinal detachment, macular oedema) and Serious Adverse Events (SAEs) in the fellow eye.
5. Frequency of ocular complications[1] in the study eye.
6. Frequency of ocular complications[1] in the fellow eye.
7. Corneal endothelial cell count change (additional safety measure) in the study eye.
8. Corneal endothelial cell count change (additional safety measure) in the fellow eye.

c) Patient self-reported outcomes at 6 weeks, 3, 6 and 12 months following surgery in the study eye:

1. Vision health status as measured by the Catquest-9SF questionnaire.
2. Quality of life as measured by the EQ-5D-3L questionnaire + vision bolt-on question (EQ-5DV)

Additional outcomes will be collected for a detailed cost and cost effectiveness analysis; however this analysis will not be performed by the Trial statistician so these outcomes are not

1. A complication will be defined as any event that causes unintentional injury to an ocular structure, or requires additional treatment, or has a negative effect on a patient's health or eyesight.

described here. Further details on the cost effectiveness analysis can be found in the Health Economic Analysis Plan.

4.3 Exploratory Outcomes

The exploratory outcomes listed below will be measured at both 3 and 12 months following surgery in the study eye unless otherwise specified. Please note that fellow eye refers to fellow eyes eligible for trial surgery that received surgery after the study eye and within 3 months of study eye surgery.

1. Spherical equivalent refraction (SER) in the study eye.
2. SER in the fellow eye.
3. Central retinal thickness (µm) in the study eye.
4. Central retinal thickness (µm) in the fellow eye.
5. Corneal and refractive astigmatism in the study eye
6. Corneal and refractive astigmatism in the fellow eye
7. UDVA, logMAR at 6weeks following surgery in the study eye (NHS records data used for multiple imputation of the primary outcome)

4.4 Scoring and deriving outcome measures

4.4.1. Distance Visual Acuity (DVA) Scoring

DVA is recorded as the number of correct letters read in the ETDRS chart. The ETDRS chart is comprised of 14 lines with 5 letters per line (i.e., 70 letters in total). With the ETDRS scoring system:

i. If twenty or more letters are read correctly at a starting distance of 4 metres, the visual acuity score is equal to the number of letters read correctly +30. If less than twenty letters are read correctly at a starting distance of 4 metres, the visual acuity score is equal to the number of letters read correctly at 4 metres plus the number of letters read correctly at 1 metre in the first six lines.

iii. If no letters are read correctly at either the 4 metre distance or the 1 metre distance, tests counting fingers (CF), hand motion (HM), perception of light (PL) and no perception of light (NPL) will be performed.

The visual acuity score will be converted to logMAR equivalents using the formula:

$$logMAR = 1.7 - 0.02 \times (Visual\ acuity\ score)$$

With this conversion a 5 letter difference in visual acuity is equivalent to a difference of 0.1 logMAR [1].

For patients that cannot read any letters correctly in the EDTRS chart at a distance of 1 metre, assessments of counting fingers (CF), hand motion (HM), perception of light (PL) and no perception of light (NPL) will be assigned VA logMAR values of 2.10, 2.40, 2.70 and 3.00 respectively. Therefore VA logMAR will range from -0.3 to 3.0 with lower values indicating better vision.

4.4.2. Spherical equivalent refraction (SER) Error

The spherical equivalent refractive error (SER) will be calculated by adding half of the cylinder power (cyl) to the sphere power:

$$SER = sphere + \left(\frac{cyl}{2}\right)$$

SER outside ±0.75D indicate degraded distance vision without glasses.

4.4.3. Intended refractive target

The percentage of patients within ±0.5 and within ±1.0D at baseline will be computed from the expected post-operative refractive outcome.

The percentage of patients within ±0.5 and within ±1.0D at 3 months and 12 months following surgery in the study eye will be computed from the spherical equivalent refraction error at 3 and 12 months respectively.

4.4.4. Astigmatism

There are two components of astigmatism:

- Corneal astigmatism which is due to the shape of the cornea
- Refractive astigmatism is the astigmatism measured by refraction and as such represents the combined effects of astigmatism caused by the shape of the cornea, the shape of the lens, the angulation of the retina and the relative positions of the lens, cornea and retina to each other (a tilted spherical lens will cause astigmatism).

The number of patients with corneal astigmatism will be based on the keratometry readings from the Pentacam corneal topography using the equation:

K1flat-K2steep ≥ ±0.75D

An absolute difference of 0.75D or more represents significant corneal astigmatism.

The number of patients with refractive astigmatism will be based on refractive cylinder. An absolute cyl of 0.75D or more represents significant refractive astigmatism.

4.4.5. Corneal endothelial cell count

A total of 3 measurements are collected per eye. These will be summarised by averaging the available measurements. Lower values indicate greater corneal endothelial damage.

4.4.6. Catquest-9SF

The Catquest-9SF is a self-reported matrix composed of 9 items within two dimensions; perceived difficulty in performing daily-life activities (7 items) and global questions about difficulties in general and satisfaction with vision (2 items), rated on 4-point scales ranging from 1 to 4 (i.e., very great difficulty=1, great difficulty=2, some difficulty=3, no difficulty=4). In addition, patients can answer “cannot decide=0”. This response category will be treated as missing.

Questionnaires will be regarded as completed if they have no more than two missing items[2]. Ordinal raw respondents’ ratings for complete questionnaires (i.e. 7 items or more) will be converted to Rasch scores using the Rasch item–category calibrations provided by the authors of the validation study[3]. A global Rasch score ranging from -4.2 to

3.7, will be obtained by computing a mean of the available items. More negative scores (or less positive) indicate less visual disability.

4.4.7. EQ-5D-3L

The EQ-5D-3L consists of a self-reported matrix comprising 5 items or dimensions (i.e., mobility, self-care, usual activities, pain-discomfort and anxiety-depression) rated on 3-point scales ranging from 0 to 2 and a self-rated health state 100mm visual analogue scale (VAS). Respondents' ratings will be combined according to manual instructions using the U.K. norms, into a single Health Utility score ranging from -0.594 to 1. Higher scores in both scales indicate better health status[4].

If the instrument has no more than one missing item, then we shall impute the missing item by the mean of the completed items and the Health Utility score will be computed. If the instrument has more than 1 missing item, then the Health Utility score will be set to missing.

The visual bolt-on currently has experimental status, so that in the absence of published validated norms the EQ-5D will be analysed without it. However, the visual bolt-on component of the questionnaires will be descriptively analysed by treatment arm.

5. DATA

5.1 CRF and variables

Full details of data collection and timing are described in the trial protocol (Version 4.0 dated 27 Sep 2016). Copies of the case report forms (CRFs) are included in the Trial Master File (TMF).

5.2 Management of datasets

At the time of analysis:

- A copy of each dataset will be prepared by the Trial or Delegated Statistician (frozen dataset) and saved in section 3 'Analysis' of the electronic Statistical Master File (eSMF).
- If necessary, data can be added to or amended in the main, unfrozen copy of the dataset.
- If any outstanding queries are resolved during the analysis that relate to data in the frozen dataset (e.g. problems that are found during analysis or amended CRFs that are return to CCTU), the main and frozen dataset should both be altered.
- If any outstanding data queries are resolved while the analysis files are being prepared (when only a practice dataset has so far been copied), the changes need only be made to the main dataset and an updated frozen copy made available in section 3 of the eSMF.

5.3 Data verification

Data verification, consistency and range checks are performed during data entry, as well as checks for missing data (copies of these checks can be found in the TMF). Additional range, consistency and missing data checks will be performed when the datasets for analysis are

constructed, as appropriate, before the statistical analysis is performed. All variables will be examined for unusual, outlying, unlabelled or inconsistent values.

Any problems with trial data will be queried with the Trial Manager or Data Manager as appropriate. If possible, data queries will be resolved; although it is accepted that due to administrative reasons and data availability a small number of problems will continue to exist. These will be minimised.

5.4 Data coding

Details of the variables, including variable coding lists are included in the metadata which forms part of the TMF.

6. SAMPLE SIZE ESTIMATION

6.1 Type of Comparison and Hypothesis

FACT is designed as a non-inferiority trial to demonstrate that Femtosecond laser-assisted cataract surgery (Femto) is not inferior to standard Phacoemulsification cataract surgery (Phaco), by assessing UDVA logMAR in the study eye measured using a standard ETDRS chart at a starting distance of 4 metres.

A change in visual acuity of 1 line of the chart is considered to be clinically important, one logMAR line is 5 letters (each letter is 0.02 logMAR). Femto cataract surgery would be regarded as non-inferior to Phaco if the UDVA, logMAR at 3 months is not more than 0.1logMAR higher in the intervention group.

The null hypothesis (H_0) is that Femto is inferior to Phaco with respect to the UDVA, logMAR at 3months:

H_0: $|\mu_{Femto} - \mu_{Phaco}| \geq 0.1$logMAR

The alternative hypothesis (H_1) is that Femto is not inferior to Phaco with respect to the UDVA, logMAR at 3 months:

H_1: $|\mu_{Femto} - \mu_{Phaco}| < 0.1$logMAR

Where: μ_{Femto} = mean UDVA, logMAR in the Femto group

μ_{Phaco} = mean UDVA, logMAR in the Phaco group

In order to conclude non-inferiority, we need to reject the null hypothesis.

6.2 Primary outcome

The primary clinical outcome is UDVA, logMAR in the study eye on the ETDRS logMAR chart at a starting distance of 4 metres at 3 months ascertained by an optometrist masked to the trial group.

If there is truly no difference in mean logMAR between the two groups, then 432 patients (216 per group) would provide 90% power to be sure that a 95% two sided confidence interval would exclude the non-inferiority limit of 0.1 logMAR, assuming a common standard deviation (SD) of 0.32. The SD is from the Royal College of Ophthalmologists' National Ophthalmic Database of unaided vision 3 months following cataract surgery (n= 20,155).

However, although treatment is delivered on an individual basis, each patient cannot be assumed to generate independent information since they will be clustered within surgeons. To take account of clustering by surgeon (i.e. the variation between surgeons in the treatment effect) the sample size must be increased by an inflation factor f = 1 + (m-1)*p. Assuming a total of 16 surgeons contribute and an average cluster size (m) of 50 (patients/surgeon) and an estimated ICC (p) of 0.012, this yields an f of 1.59. A total of 688 patients (344 per group) would enable the trial to take account of clustering by surgeon. To allow for an anticipated 15% dropout rate (the mean age of patients undergoing cataract surgery is 75 years old and many have significant systemic comorbidities) the total sample size required is 808 patients (404 per group).

6.3 Secondary outcomes

The trial is not powered to detect differences between the two randomised groups for secondary effectiveness or safety endpoints.

7. ANALYSIS PRINCIPLES

7.1 Intention-to-treat (ITT) or per-protocol?

To retain the validity of the randomisation process all analyses relating to the study eye will be by intention-to-treat (ITT), where all randomised patients are analysed in their allocated group whether or not they received their allocated treatment. In addition, we will conduct a per-protocol (PP) analysis for the primary outcome as recommended for non-inferiority trials[5]. The per-protocol analysis will include all patients that received their allocated treatment.
Only if both ITT and PP analyses support non-inferiority will the trial be considered positive.
Fellow eye data will be analysed for the eligible fellow eyes that received surgery after the study eye and within 3 months of study eye surgery. Fellow eyes will be analysed by treatment received.
If ITT and PP analyses differ, complier average causal effect analysis (CACE) may beconsidered for the primary outcome to mitigate uncertainty [6].

7.2 Significance level of tests

All confidence intervals will be 95% and two-sided. Statistical tests will use a two-sided *p* value of 0.05, unless otherwise specified. There will be no formal adjustment of *p* values for any interim analyses performed.

7.3 Baseline comparability

Baseline characteristics will be summarised by randomised group. No formal statistical comparisons will be performed. Please note that, except for baseline intended refractive target (please see section 4.4.3), baseline refers to any parameters measured at either the surgical pre-assessment visit (visit 1 Baseline CRF) or at randomisation prior to surgery (visit 2 Randomisation CRF).

7.4 Adjustment for design factors

Since randomisation was stratified by treatment centre, surgeon and whether in the local clinician's opinion the patient will require surgery on one or both eyes, analyses of continuous outcomes and binary outcomes with enough events to fit logistic regression models, will involve adjustment for these three factors (as recommended in ICH E9, 5.7). Treatment effects are then estimated conditional on treatment centre, surgeon and whether the patient will require surgery on one or both eyes (note that surgeon refers to the individual surgeon, not the surgeon grade). The model for the primary analysis will also be adjusted for baseline habitual logMar[2] visual acuity values. Similar adjustments will be made for any continuous secondary outcomes if a baseline value is recorded.

Astigmatism is the biggest possible confounding variable in interpreting visual acuity outcomes and therefore baseline absolute difference between the keratometry readings from the Pentacam corneal topography using the equation: |K1flat-K2steep| (see section 4.4.4) will be incorporated as an adjustment factor in the analysis of visual acuity outcomes. Surgeon will be included in the model as a random effect with an additional random treatment by surgeon interaction term (if possible) to take account of clustering by surgeon and variation in the treatment effect by surgeon.

Adjustment for design factors will not be made for binary secondary safety outcomes with too few events to use parametric methods.

7.5 Follow-up and losses to follow-up: handling missing data

Missing values for baseline covariates will be dealt with using mean imputation within centre[7]. Any missing values for a baseline covariate X will be replaced with the overall mean observed X. Mean imputation is an appropriate method because randomisation means baseline variables are independent of treatment group.

Missing observations in the primary outcome will be dealt with using multiple imputation by chained equations (MICE). Multiple imputation (MI) is one of the recommended methods for imputing missing data in RCTs[8]. This method attempts to mitigate for missing data by replacing ('imputing') unobserved data with values estimated from a model based on observed values of variables which may be predictive of those values which are unobserved. To account for additional uncertainty introduced by estimating the missing values, the process is repeated a number of times and each of the resulting imputed datasets are separately analysed, hence the term 'multiple imputation'. The results are combined in a way that accommodates the additional variability due to the estimation process, hence improving inference. The process is consistent with the missing at random (MAR) assumption, in essence the data available for patients before they drop out will be used to predict the endpoint. The chained equations procedure (CE) is a practical approach to MI where several variables with missing values are imputed in turn, hence the term 'chained equations'. Full details of the MI model(s) are described in section 8.4.6.

Reasons for missingness may be important and these will be investigated using logistic regression of covariates on an indicator of missingness.

2. Visual acuity (logMAR) with the patient's usual method of correction (current glasses or unaided).

Sensitivity analysis will investigate the validity of the MAR assumption and address the impact of missing data for all patients (see section 8.4.2).

7.6 Summarising models

Where possible, analysis of outcomes will involve a parametric model. Treatment effect estimates will be presented as regression coefficients and 95% confidence intervals.

8. ANALYSIS DETAILS

The results of the analyses will be reported following the principle of the ICH E3 guidelines on the Structure and Content of Clinical Study Reports.

8.1 Recruitment and follow-up patterns

Recruitment will be presented by year and treatment centre.

The number of CRFs completed – excluding patients who have been withdrawn and were unwilling to continue follow up will be reported by treatment arm.

The number of patients who have been withdrawn, were unwilling to continue follow-up or died while on study will be reported by treatment arm.

8.2 Baseline Characteristics

Baseline characteristics will be reported for each treatment arm. Summary measures for the baseline characteristics of each group will be presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

8.3 Trial treatment

The number of patients not receiving their allocated surgery for the study eye and reason(s) for not receiving it will be summarised by treatment group.
The number of patients not receiving their allocated surgery for the fellow eye and reason(s) for not receiving it, and the time since surgery on the study eye will be summarised by treatment group.

8.4 Analysis methods

Analysis of the primary outcome will be performed on imputed datasets (see sections 7.5 and 8.4.7); in addition a complete case analysis of the primary oucome will be performed. If there is no substantial difference between the primary outcome from the imputed data and the complete case data, all secondary outcomes will be performed on complete cases only.

8.4.1. Primary analysis

We shall use a linear mixed-effects model to estimate the difference in UDVA logMAR between the two treatments (Femto – Phaco) at 3 months, together with a two-sided 95% confidence interval, adjusting for baseline habitual logMar visual acuity and the randomisation stratifiers (i.e., centre, surgeon, and whether or not patients have one or both eyes eligible). We will include surgeon in our model as a random effect (random

intercept) to account for clustering by surgeons. The model will be fitted using REstricted Maximum Likelihood (REML).

Results will be presented as the mean difference with its corresponding 95% CI.

If the upper end of the 95% CI for the difference between treatment means does not cross the non-inferiority limit of 0.1 logMAR, then Femto cataract surgery will be regarded as non-inferior. If the mean difference is negative and its 95% CI lies wholly to the left of zero, then we can conclude that Femto cataract surgery is superior to Phaco cataract surgery (see A in the figure below). We will perform sequential testing of the non-inferiority and superiority hypotheses.

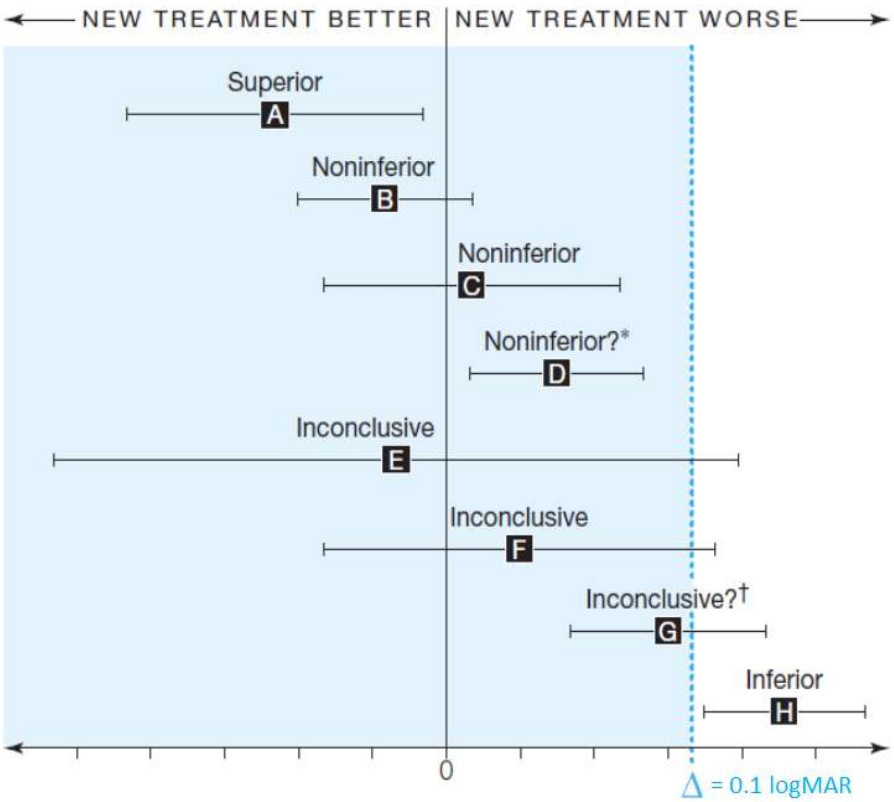

Figure 1. Error bars indicate 2-sided 95% CIs. The dashed line indicates the non-inferiority margin; the shaded region indicates the zone of inferiority.

*This CI indicates non-inferiority in the sense that it does not include Δ, but the new treatment is significantly worse than the standard. Such a result is unlikely because it would require a very large sample size.

†This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard. Adapted from Piaggio et al[9]

In addition we will report the intracluster correlation coefficient (ICC), number of clusters (i.e., how many surgeons contribute) and the average cluster size (i.e., number of operations performed per surgeon).

8.4.2. Sensitivity analyses

The primary analysis will be performed on imputed datasets. We will repeat the primary analysis on a dataset containing the observed trial data only to investigate how robust the

analysis is to the MAR assumption. If the MAR assumption does not appear robust further sensitivity analysis under MNAR may be considered such as a pattern-mixture model approach. If the sensitivity analysis shows that the overall results and conclusions of the trial are not affected by the assumptions made, the findings can be viewed with a higher degree of confidence. However if the sensitivity analysis identifies particular decisions or missing information that greatly influence the findings of the trial, further sensitivity analysis may be considered to determine how much missing values would need to differ in order to change the results of the main trial, and the statisticians will discuss the findings and seek advice from the Trial Steering Committee (TSC) to resolve uncertainties and obtain extra information. If this cannot be achieved, the results must be interpreted with an appropriate degree of caution. Such findings may generate proposals for further investigations and future research.

8.4.3. Secondary analyses

As stated in section 6.3 the trial is not powered to detect differences between the two randomised groups for secondary effectiveness or safety outcomes. Therefore, for secondary outcomes the differences between the two groups will be summarised using estimates and confidence intervals.
Secondary analyses will be performed and reported in two stages, after completing all the first and after completing all the last trial follow-up visits (i.e. at 3, and at 12 months following surgery in the study eye).
Please note, for cases where both eyes were eligible to undergo surgery, there is no guarantee that the fellow eye received the same intervention as the study eye (patients can express a wish not to receive the same intervention in the fellow eye). Given the observational nature of fellow eye data, respective outcomes will be presented by treatment received and for the subgroup of patients that underwent surgery in the fellow eye within 3 months of surgery in the study eye. Time between study eye surgery and fellow eye surgery will be summarised.

a) Continuous secondary clinical outcomes

<u>Short term outcomes</u>

Each of the following continuous secondary clinical outcome measures at 3 months following surgery in the study eye:

1) UDVA, logMAR in the fellow eye and with both eyes open using the ETDRS chart at a starting distance of 4 metres.
2) CDVA, logMAR in the study eye, fellow eye and with both eyes open using the ETDRS chart at a starting distance of 4 metres.
3) Corneal endothelial cell count change from baseline in the study eye, and fellow eye.

will be analysed separately for study eye, fellow eye and both eyes open using linear mixed-effects models to estimate the differences between the two treatments (Femto – Phaco). As for the primary analysis model, stratification variables (i.e., treatment centre, surgeon, and whether or not patients have one or both eyes eligible) will be included as covariates in the model(s). Surgeon will be included in model(s) as a random effect.

Distance visual acuity outcomes for the study eye, whether they are unaided or corrected, will be adjusted for baseline habitual logMar visual acuity. Note that baseline visual acuity was not measured for the fellow eye. The achieved post-operative spherical equivalent refraction error will be adjusted for the expected post-operative refractive error, whilst the remaining continuous outcomes will be adjusted for their own baseline values if available.

Long term outcomes

To estimate the differences between the two treatment groups for the same outcomes at 12 months following surgery in the study eye, the linear mixed-effects models described for the 3 months analyses will be extended to include another two fixed effects; the 'timepoint' (i.e., factor with two levels; 3 months and 12 months), and the treatment by timepoint interaction term to assess whether there any differences in outcome(s) across timepoints. A random patient effect will be included in the model(s) to take account of clustering by patient. A random surgeon effect will be included in the model(s) to take account of clustering by surgeon.

All the models will be fitted using REML. Estimates of treatment effects with 95% CIs will be presented.

b) Continuous secondary patient self-reported outcomes

Short term outcomes

Each of the following continuous secondary patient self-reported outcomes at six weeks and 3 months following surgery in the study eye:

- Catquest-9SF.
- EQ-5D-3L.

will be analysed using linear mixed-effects models to estimate the differences between the two treatments (Femto-Phaco) at each time point.. Each model will be adjusted for stratification variables (i.e., treatment centre, surgeon, and whether or not patients have one or both eyes eligible), nand baseline values. A random surgeon effect will be included in the model(s) to take account of clustering by surgeon.

Long term outcomes

We will estimate differences in the patient self-reported outcomes between the two treatments groups at 12 months following surgery in the study eye in the same fashion as for 3 months.

All the models will be fitted using REML. Estimates of treatment effects with 95% CIs will be presented.

c) Binary Secondary Outcomes with baseline values

Short term outcomes

The proportion of patients who at 3 months following surgery in the study eye are:

- Within ±0.5 dioptres of intended refractive outcome in the study eye, and fellow eye
- Within ±1.0 dioptres of intended refractive outcome in the study eye, and fellow eye

will be analysed separately for study eye and fellow eye using mixed-effects logistic regression models adjusting for stratification variables (i.e. treatment centre, surgeon, and whether or not patients have one or both eyes eligible) and the expected post-operative refractive error. Surgeon will be included in model(s) as a random.

Long term outcomes

The same outcomes will be analysed at 12 months. The mixed-effects logistic regression models described for the 3 months analyses will be extended to include another two fixed effects; the 'timepoint' (i.e., factor with two levels; 3 months and 12 months), and the treatment by timepoint interaction term to assess whether there any differences in outcome(s) across timepoints, and a random patient effect to take account of clustering by patient.

Treatment effect estimates will be transformed back from their logistic form and reported as odds ratios (OR) with their corresponding 95% CIs.

d) Binary Secondary Outcomes with no baseline values

Differences between the two treatment arms (Femto – Phaco) for the following safety binary outcomes:

- Proportion of intra-operative events in the study and fellow eyes.
- Proportion of Adverse Events and Serious Adverse Events (SAEs) within 3 months in the study and fellow eyes.
- Proportion of complications within 3 months in the study and fellow eyes.
- Proportion of Adverse Events and Serious Adverse Events (SAEs) within 12 months in the study and fellow eyes.
- Proportion of ocular complications within 12 months in the study and fellow eyes.

These binary outcomes will be analysed separately for study eye and fellow eye using Fisher's exact tests as it is unlikely there will be enough events to fit logistic regression models. Summary measures will be frequency and proportion of patients with an event in each group. Treatment effects will be estimated by the difference in event rates and 95% CI for the differences.

8.4.4. Exploratory analyses

The exploratory clinical outcome measures listed below will be analysed separately for study eye and fellow eye using linear mixed-effects models in the same way as for secondary continuous outcomes. Given the observational nature of fellow eye data, respective outcomes will be presented by treatment received and for the subgroups of patients that underwent surgery in the fellow eye within 3 months of surgery in the study eye. Analyses will be conducted separately at 3 and 12 months following surgery in the study eye:

1) Spherical equivalent refraction (SER) in the study eye, and fellow eye.
2) Central retinal thickness (μm) in the study eye, and fellow eye.

8.4.5. Regression diagnostics

The regression models are built on assumptions about random effects distributions, correlation structure and residuals that need careful consideration. We will plot:

- Histograms and probability plots to assess normality.
- Scatterplots of residuals against fitted values to assess constant variance and linearity, and to identify potential outliers

for the different levels of residuals. Patients (level-1 residuals) clustered within surgeons (level-2 residuals) for models with two levels, and timepoint measurements (level-1) clustered within patients (level-2 residuals), and patients clustered within surgeons (level-3 residuals) for 3 level models.

Should the normality assumption be untenable for any continuous outcomes (including after log transformation), a non-parametric method will be undertaken using change from baseline as a sensitivity analysis, although covariate adjustments will not be possible.

8.4.6. Subgroup analyses

A planned subgroup analysis will be conducted to investigate whether the primary analysis differs according to whether or not surgery was required on both eyes. Subgroup analysis will be performed for the primary outcome only, by adding an interaction term to the model for the primary outcome. This will consist of one interaction term:

- Trial treatment and whether or not surgery was required on both eyes

We will report separate estimates and confidence intervals for each patient subgroup.

8.4.7. Multiple imputation by chained equations (MICE)

To avoid bias and loss in efficiency, missing primary outcome values will be imputed using MICE[10] under the assumption that missing data values are likely to be missing at random (MAR) which means they are dependent on the values of the observed data, but not dependent on the values of the missing data.

Reasons for missingness in the primary outcome may be important and these will be investigated using logistic regression of baseline covariates on an indicator of missingness at 3 months.

The sample size estimation assumed 15% of patients would not contribute to primary outcome data, therefore at least 15 imputed datasets will be drawn and analysed separately for each randomised group, replacing missing outcome values with simulated values from a set of imputation models containing all potential prognostic baseline covariates (i.e., age, gender, presence of ocular co-pathology, astigmatism), presence of intra-operative complications, the primary outcome variable (i.e., UDVA logMAR at 3 months), clinical secondary outcomes at 3 months for the study eye, if available (i.e., corrected and uncorrected DVA logMAR, spherical equivalent refraction error, central retinal thickness (µm), , corneal endothelial cell count and presence of ocular complications), , as well as stratification factors (i.e., treatment centre, , and whether or not patients have one or both eyes eligible), and randomised treatment allocation To make the MAR assumption more plausible post-operative distance visual acuity at 6 weeks obtained from NHS records will also be included in the imputation model together with any other variables found to be strongly predictive of missingness in the reasons for missingness logistic regression analysis. Please note that visual acuity data from NHS records may be collected in Snellen and therefore such data will be converted to logMAR as per conversion table found at https://www.rcophth.ac.uk/patients/snellen-and-logmar-

acuity-testing/. If different values of logMAR correspond to the same value of Snellen we will use the average of the logMAR values corresponding to the Snellen value.

Missing values for continuous outcomes will be imputed from linear regression models, missing values for binary variables will be imputed from binary logistic models[11]. Results from the imputed datasets will be combined using Rubin's rules[12].

MI model diagnostics

To assess the extent to which imputed values differ from observed values we will produce:

- Summary statistics of the observed and imputed data to explore differences in means and standard deviations between the observed and imputed values[13].
- Scatterplots of residuals against fitted values of each imputed dataset. Similar patterns across datasets will be an indication of the suitability of the imputation model(s).

9. TABLES AND GRAPHS

9.1 Tables

Table 1: Number of patients screened but not enrolled and reasons* not enrolled by centre

	Centre†			
	MEH	**SEH**	**NCH**	**Total**
Total patients screened				
Reasons for exclusions*				
Eyes with corneal ring and/or inlay implant(s), or severe corneal opacities, corneal abnormalities, significant corneal oedema or diminished aqueous clarity that is likely to obscure OCT imaging of the anterior lens capsule				
Adult not aged 18 or over with visually symptomatic cataract in one or both eyes				
Not sufficiently fluent in English for informed consent and completion of the health state questionnaires				
Post-operative intended refractive target in the study eye is not within +/-0.5 D emmetropia				
Descemetocele with impending corneal rupture				
Poor pupil dilation that is expected to require surgical iris manipulation				
Subluxed crystalline lens				
Patient unable to give consent				
Patient not willing to attend follow up 3 and 12 months after cataract surgery in the study eye				
Patient unable to be positioned for surgery				
Patient scheduled to undergo combined surgery e.g. cataract and trabeculectomy				
Any contraindications to cataract surgery				
Any clinical condition which the investigator considers would make the patient unsuitable for the trial, including pregnancy				
Other				
Total eligible				
Refused consent				
Total withdrawn prior to randomisation				
Randomised				

**Only one reason is tabulated for each patient*

†MEH= St Ann's at Moorfields Eye Hospital, SHE=Sussex Eye Hospital, NCH=New Cross Hospital

Table 2: Number of patients randomised by month and centre

		Centre[†]			
Year	**Month**	**MEH**	**SEH**	**NCH**	**Total**
2015	May				
	June				
	July				
	August				
	September				
	October				
	November				
	December				
2016	January				
	February				
	March				
	April				
	May				
	June				
	July				
	August				
	September				
	October				
	November				
	December				
2017	January				
	February				
	March				
	April				
	May				
	June				
	July				
	August				
	September				
Total					

[†] *MEH= St Ann's at Moorfields Eye Hospital, SHE=Sussex Eye Hospital, NCH=New Cross Hospital*

Table 3a: Baseline characteristics of trial patients by allocated treatment – Study eye

		Femto (N=)	Phaco (N=)
Demographics			
Gender, n (%)	Male		
	Female		
Age (years)	Mean (SD)		
Study eye, n (%)	Right		
	Left		
Ethnicity, n (%)	White		
	Mixed		
	Asian or Asian British		
	Black or Black British		
	Other Ethnic Groups		
Stratification variables			
Eyes eligible for surgery, n (%)	One eye		
	Both eyes		
Surgeon grade, n (%)	Consultants		
	Fellows		
	Assoc Spec or Staff Grade		
	Specialist trainees (any level)		
Centre[1], n (%)	MEH		
	SEH		
	NCH		
Pre-operative astigmatism			
Corneal astigmatism[2], n (%)	<0.75D		
	0.75D to 2.0D		
	≥ 2.0D		
Corneal astigmatism[2] (dioptre)	Mean (SD)		
Axial Length (mm)	Mean (SD)		
Refractive astigmatism[2], n (%)	<0.75D		
	0.75D to 2.0D		
	≥ 2.0D		
Expected postoperative refractive outcome (refractive astigmatism)[2] (dioptre)	Mean (SD)		
Intended refractive target (dioptre), n (%)	Within ±0.50D		
	Within ±1.00D		
Central retinal thickness (µm)	Mean (SD)		
Ocular co-pathology [3], n (%)	Present		
	Absent		
Type of ocular co-pathology, n	Glaucoma		
	Diabetic retinopathy		
	Brunescent or white cataract		
	No fundal view or vitreous opacities		
	Pseudoexfoliation or phacodonesis		
	Previous vitrectomy		
	Age Related Macular Degeneration		
	High myopia (more than -6D)		
	Amblyopia		
	Corneal pathology		
	Other ocular co-pathology		
	Previous cataract surgery		

Table3a (continued)

		Femto (N=)	Phaco (N=)
Visual acuity			
Habitual UDVA, logMAR[4]	Mean (SD)		
Safety			
Preoperative corneal endothelial cell count (cells/mm^2)	Mean (SD)		
Quality of life			
Catquest–9SF	Mean (SD)		
EQ 5D 3L: Health Utility	Mean (SD)		
EQ 5D 3L Health State: VAS	Mean (SD)		
EQ 5D 3L: vison bolt-on, n (%)	I have no problems seeing		
	I have some problems seeing		
	I have extreme problems seeing		

[1]MEH= St Ann's at Moorfields Eye Hospital (St. Ann's), SEH=Brighton & Sussex University Hospital (Sussex Eye), NCH= The Royal Wolverhampton (New Cross Hospital)

[2]Absolute values

[3]Number of patients with at least one co-pathology.

[4]Visual acuity (logMAR) with the patient's usual method of correction (current glasses or unaided).

Table 3b: Baseline characteristics of trial patients by treatment received – Fellow eye

		Femto (N=)	Phaco (N=)
Demographics			
Gender, n (%)	Male		
	Female		
Age (years)	Mean (SD)		
Fellow eye, n (%)	Right		
	Left		
Ethnicity, n (%)	White		
	Mixed		
	Asian or Asian British		
	Black or Black British		
	Other Ethnic Groups		
Stratification variables[1]			
Surgeon grade, n (%)	Consultants		
	Fellows		
	Assoc Spec or Staff Grade		
	Specialist trainees (any level)		
Centre[2], n (%)	MEH		
	SEH		
	NCH		
Pre-operative astigmatism			
Corneal astigmatism[3], n (%)	<0.75D		
	0.75D to 2.0D		
	≥ 2.0D		
Corneal astigmatism[3] (dioptre)	Mean (SD)		
Axial Length (mm)	Mean (SD)		
Refractive astigmatism[3], n (%)	<0.75D		
	0.75D to 2.0D		
	≥ 2.0D		
Expected postoperative refractive outcome (refractive astigmatism)[3] (dioptre)	Mean (SD)		
Intended refractive target (dioptre), n (%)	Within ±0.50D		
	Within ±1.00D		
Central retinal thickness (μm)	Mean (SD)		
Fellow eye surgery			
Fellow eye received the allocated study eye treatment, n (%)	Yes		
	No		
Time from previous study eye cataract surgery to fellow eye surgery, (days)	Median (IQR)		
Ocular co-pathology [4], n (%)	Present		
	Absent		
Type of ocular co-pathology, n	Glaucoma		
	Diabetic retinopathy		
	Brunescent or white cataract		
	No fundal view or vitreous opacities		
	Pseudoexfoliation or phacodonesis		
	Previous vitrectomy		
	Age Related Macular Degeneration		
	High myopia (more than -6D)		
	Amblyopia		
	Corneal pathology		
	Other ocular co-pathology		
	Previous cataract surgery		

Table 3b (continued)

		Femto (N=)	Phaco (N=)
Safety			
Preoperative corneal endothelial cell count (cells/mm^2)	Mean (SD)		
Quality of life			
Catquest–9SF	Mean (SD)		
EQ 5D 3L: Health Utility	Mean (SD)		
EQ 5D 3L Health State: VAS	Mean (SD)		
EQ 5D 3L: vison bolt-on, n (%)	I have no problems seeing		
	I have some problems seeing		
	I have extreme problems seeing		

[1]Both eyes have to be eligible and therefore we are not presenting data relating to "Eyes eligible for surgery"
[2]MEH= St Ann's at Moorfields Eye Hospital (St. Ann's), SEH=Brighton & Sussex University Hospital (Sussex Eye), NCH= The Royal Wolverhampton (New Cross Hospital)
[3]Absolute values
[4]Number of patients with at least one co-pathology.

Table 4: Frequency of intra-operative complications by treatment allocated (study eye) or by treatment received (fellow eye)

	Femto (N=)	Phaco (N=)	Effect (Femto – Phaco) Difference (95% CI)
Study eye			
Intra-operative complications[†], n/N (%)			
Reported intra-operative complications, n			
Anterior capsule tear			
Posterior capsule tear with vitreous loss			
Posterior capsule tear no vitreous loss			
Intra-operative pupil constriction needing intervention			
Dropped lens fragments or nucleus			
Choroidal haemorrhage			
Zonular dialysis			
Failure to dock laser			
Aborted or incomplete laser delivery			
Incomplete capsulotomy identified in surgery, requiring manual completion			
Laser delivery to inappropriate structure of eye			
Other			
Fellow eye			
Intra-operative complications[†], n/N (%)			
Reported intra-operative complications, n			
Anterior capsule tear			
Posterior capsule tear with vitreous loss			
Posterior capsule tear no vitreous loss			
Intra-operative pupil constriction needing intervention			
Dropped lens fragments or nucleus			
Choroidal haemorrhage			
Zonular dialysis			
Failure to dock laser			
Aborted or incomplete laser delivery			
Incomplete capsulotomy identified in surgery, requiring manual completion			
Laser delivery to inappropriate structure of eye			
Other			

[†]*Number of patients with one or more complications.*

Table 5a: Results of the regression models adjusted for stratification variables and baseline values and safety events at 3 months – Study eye

		Femto (N=)	Phaco (N=)	Effect (Femto – Phaco) Difference (95% CI)	p-value
PRIMARY OUTCOME					
UDVA, logMAR	Mean (SD)				
SECONDARY OUTCOMES					
Distance visual acuity					
UDVA, logMAR – both eyes open	Mean (SD)				
CDVA, logMAR	Mean (SD)				
CDVA, logMAR – both eyes open	Mean (SD)				
Refractive data					
Achieved refractive target (dioptre) Within ±0.50D	 n (%)				
Within ±1.00D	n (%)				
Quality of life					
Catquest–9SF	Mean (SD)				
EQ 5D 3L: Health Utility	Mean (SD)				
EQ 5D 3L Health State: VAS	Mean (SD)				
EQ 5D 3L vison bolt-on: - I have no problems seeing - I have some problems seeing - I have extreme problems seeing	n (%)			N/A	N/A
Safety					
Corneal endothelial cell loss (cells/mm^2)	Mean (SD)				
Postoperative AEs, *patients with at least one event*	n (%)				
Expected:	n				
Post-operative uveitis	n				
Endophthalmitis	n				
Vitreous to wound	n				
Retinal tear or retinal detachment	n				
Elevated intraocular pressure requiring treatment	n				
Medication allergy or intolerance	n				
Macular oedema	n				
Corneal oedema	n				
Other ocular surgery	n				
Unexpected:	n				

Posterior vitreous detachment	n				
Cracked/damaged IOL	n				
Capsular block	n				
Posterior capsule opacification	n				
Corneal abrasion	n				
Cataract remnant post-op	n				
IOL subluxation	n				
Other ocular	n				
SAEs, *patients with at least one event*	n (%)				
EXPLORATORY OUTCOMES					
Central retinal thickness (µm)	Mean (SD)				
Spherical equivalent (dioptre)	Mean (SD)				
Corneal astigmatism (dioptre)	n (%)				
Refractive astigmatism (dioptre)	n (%)				
UDVA 6 weeks post-surgery, logMAR (NHS records)	Mean (SD)				

Table 5b: Results of the regression models adjusted for stratification variables and safety events at 3 months – Fellow eye

		Femto (N=)	**Phaco (N=)**	**Effect (Femto – Phaco) Difference (95% CI)**	**p-value**
PRIMARY OUTCOME					
UDVA, logMAR	Mean (SD)				
SECONDARY OUTCOMES					
Distance visual acuity					
UDVA, logMAR – both eyes open	Mean (SD)				
CDVA, logMAR	Mean (SD)				
CDVA, logMAR – both eyes open	Mean (SD)				
Refractive data					
Achieved refractive target (dioptre) Within ±0.50D	n (%)				
Within ±1.00D	n (%)				
Quality of life					
Catquest–9SF	Mean (SD)				
EQ 5D 3L: Health Utility	Mean (SD)				
EQ 5D 3L Health State: VAS	Mean (SD)				
EQ 5D 3L vison bolt-on: - I have no problems seeing	n (%)			N/A	N/A

- I have some problems seeing - I have extreme problems seeing					
Safety					
Corneal endothelial cell loss (cells/mm^2)	Mean (SD)				
Postoperative AEs, *patients with at least one event*	n (%)				
Expected:	n				
Post-operative uveitis	n				
Endophthalmitis	n				
Vitreous to wound	n				
Retinal tear or retinal detachment	n				
Elevated intraocular pressure requiring treatment	n				
Medication allergy or intolerance	n				
Macular oedema	n				
Corneal oedema	n				
Other ocular surgery	n				
Unexpected:	n				
Posterior vitreous detachment	n				
Cracked/damaged IOL	n				
Capsular block	n				
Posterior capsule opacification	n				
Corneal abrasion	n				
Cataract remnant post-op	n				
IOL subluxation	n				
Other ocular	n				
SAEs, *patients with at least one event*	n (%)				
EXPLORATORY OUTCOMES					
Central retinal thickness (µm)	Mean (SD)				
Spherical equivalent (dioptre)	Mean (SD)				
Corneal astigmatism (dioptre)	n (%)				
Refractive astigmatism (dioptre)	n (%)				

Note that tables 5a and 5b will also be produced for the 12 month results

9.2 Graphs

G1: CONSORT flow chart.
G2: Non-inferiority graph.
G3: Profile plots with error bars by treatment allocated for effectiveness outcomes.
G4: Standard Graphs (please see example bellow) for Reporting Refractive Surgery[14]

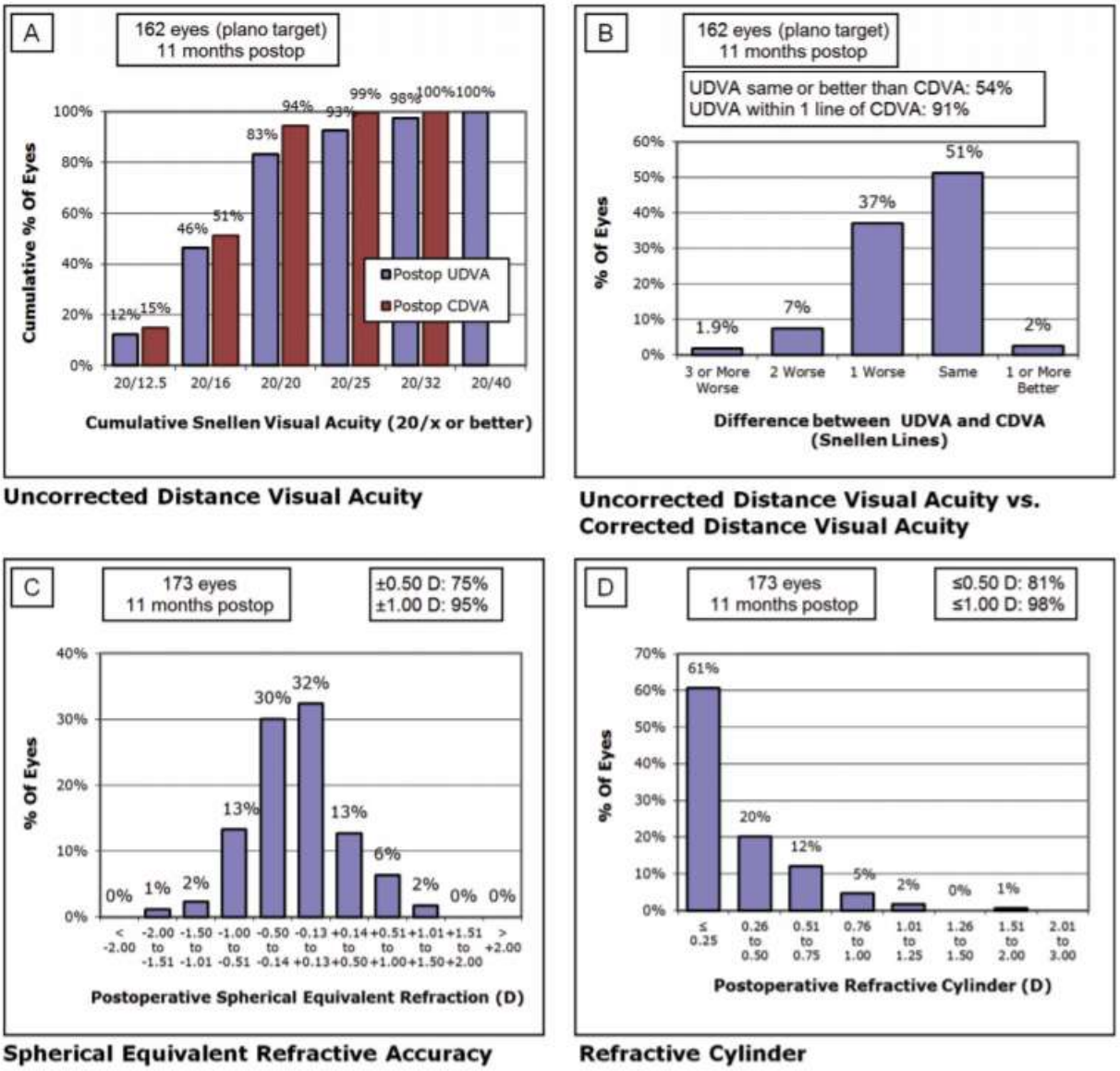

Figure 1. Standard graphs for reporting refractive outcomes for intraocular lens–based procedures in a cataract population. *A*: Uncorrected distance visual acuity. *B*: Uncorrected distance visual acuity versus corrected distance visual acuity. *C*: Spherical equivalent refraction accuracy. *D*: Postoperative refractive cylinder (CDVA = corrected distance visual acuity; UDVA = uncorrected distance visual acuity).

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Summary of changes to statistical analysis plan

Change number	Protocol version	Updated SAP version no.	Section number(s) changed	Description of and reason for change	Date changed	Actioned by	Authorised by
1.	Version 4.0	Version 2.0	8.4	References to multiple imputation for secondary outcomes *Since the SAP was finalised, we have consolidated our understanding of analysis in the presence of missing data in the RCT context, largely due to work by Ian White and others published in 2018.*[11]	09 December 2018	Kate Bennett (Trial statistician)	Nick Freemantle (Director)
2.	Version 4.0	Version 2.0	8.4 throughout	References to "additional random treatment by surgeon interaction term, (random intercept and slope) to take account of any variation in the treatment effect between surgeons." *This is not compliant with the principles of ICH E9.*	09 December 2018	Kate Bennett (Trial statistician)	Nick Freemantle (Director)
3.	Version 4.0	Version 2.0	8.4 throughout	References to "unstructured covariance matrix". *This is not required with a single random intercept model (following on from 3. above)*	09 December 2018	Kate Bennett (Trial statistician)	Nick Freemantle (Director)
4.	Version 4.0	Version 2.0	8.4.3	Analysis of health utility separately at each time point.	09 December 2018	Kate Bennett	Nick Freemantle

				A model including the health utility at each time point is included in the long term outcomes (completed at 12 months).		(Trial statistician)	(Director)
5.	Version 4.0	Version 2.0	8.4.7	Some items were not included in the multiple imputation model for the primary outcome. These included fellow eye outcomes, both eyes open outcomes, proportion of patients within 0.5 and 1.0D of intended refractive outcome. *These terms were not required in the imputation model either because these outcomes were not analysed using multiply imputed datasets or because their inclusion prevented model convergence.*	09 December 2018	Kate Bennett (Trial statistician)	Nick Freemantle (Director)
6.	Version 4.0	Version 2.0	8.4.7	Randomised treatment allocation was included in the multiple imputation model and "Imputation will be carried out separately for each randomised group" was removed. *Work by Ian White et al questions the rationale behind this approach when there is no interaction with treatment allocation included in the model.* [11]	09 December 2018	Kate Bennett (Trial statistician)	Nick Freemantle (Director)