Descemets Endothelial Thickness Comparison Trial
Statistical Analysis Plan

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DETECT Statistical Analysis Plan

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1. Background
Descemets Endothelial Thickness Comparison Trial (DETECT) is a randomized, double-masked, two-arm clinical trial. The purpose of this study is to determine which of two types of corneal transplant surgeries has the better visual outcome. Study participant's eyes will be randomized to one of two treatment groups – 1.) Ultrathin Descemet's Stripping Endothelial Keratoplasty (DSAEK) or 2.) Descemet's Membrane Endothelial Keratoplasty (DMEK).

2. Sample Size and Randomization
We anticipate that 25 eyes per arm would provide 80% power to detect a 0.12 logMAR difference (approximately 1.2 Snellen lines), assuming two-tailed alpha, and a standard deviation of best spectacle-corrected visual acuity (BSCVA) at 6 months of 0.12 logMAR (approximately 1.2 Snellen lines) at 6 months. Participant's eyes will be randomized using random block sizes in Microsoft Excel (KJR).

3. Baseline Characteristics
Baseline characteristics between the 2 arms will be compared using Fisher exact test for categorical variables and Wilcoxon rank sum test for continuous variables.

4. Primary Analysis
For the primary study analysis, we will compare BSCVA between the two groups at the 6-month time period (between 5-7 months) using ANCOVA, with baseline BCVA and treatment group as covariates. Statistical significance will be assessed by permutation with a two-sided alpha of 0.05. (If the correlation coefficient between baseline BCVA and 6 month BCVA has magnitude less than 0.1, we will omit the variable entirely, yielding a post-test only analysis).

As a methodological sensitivity analysis, we will conduct ANCOVA with ranks (which becomes the Wilcoxon rank sum test in the post-test only case). Model checking will be conducted for the primary analysis (and for all secondary analyses) based on analysis of residuals versus fitted values. We will conduct leave-one-out influence analysis to locate highly influential observations (a procedure we will apply to secondary analyses also). Individuals with missing six month data will be included based on last observation carried forward from the 3 month records; individuals with no follow-up data cannot be included but will be tabulated. Sensitivity analysis of missing values will be conducted to assess the range of values of missing observations that would be needed to change the results of the hypothesis test.

Protocol for measuring BCSVA is outlined in the MOP. BSCVA will be analyzed using an intent to treat analysis, with all eyes that are randomized being analyzed at 6 months regardless of subsequent surgery or graft failure. We will tabulate results by study site.

One safety analysis will be performed. No interim efficacy or futility analysis will be conducted.

5. Secondary Analyses

Key secondary outcomes

- We will analyze endothelial cell counts controlling for baseline endothelial cell count measured at the eye bank using mixed effect multiple linear regression conducted
- NEI-VFQ will be compared between the two groups with multiple linear regression, controlling for baseline VFQ.
- Three-month BCVA will be analysed using the same procedure as the primary outcome.
- A linear mixed model will be used in which both three and six month data are modeled, with a random intercept for eye, and with time, baseline BCVA, and treatment assignment as fixed effects. A graft rejection episode will be defined as loss of graft clarity due to edema with evidence of inflammation such as anterior chamber cell or keratic precipitates, and will be compared between the two groups using Fisher's exact test.
- For the purposes of this study, primary graft failure will be defined as a lack of graft clearing or need for re-graft within the first 2 months, and will be compared between the two groups using Fisher's exact test.

Supplementary secondary outcomes

- A pre-specified non-inferiority threshold is set at a 0.1 logMAR difference in visual acuity.
- We will also look at BSCVA at using a last observation carried forward (LOCF) analysis. For study participants who experience primary graft failure and must undergo re-graft, graft failure will be noted and a BSCVA will be performed prior to performing further surgery. This last observation will be carried forward as the 6 month BSCVA.
- We will conduct the Kolmogorov-Smirnoff test to compare the 6-month (BSCVA) distribution between DMEK and DSAEK arms.
- Interface haze as measured by Pentacam densitometry will be analyzed using a Wilcoxon rank sum test.
- Corneal higher-order aberrations as measured by Pentacam will be analyzed using a Wilcoxon rank sum test.
- We will also perform a cost-effectiveness analysis of the clinical trial data, according to the protocol provided in the Supplementary Cost Effectiveness Analysis Statistical Analysis Plan.

6. Other Data

Other data to be collected include manifest refraction, graft thickness as measured by OCT, pachymetry, operative times, and adverse events or complications.