Cover Page for Protocol, Statistical Plan and ICF

Official Title:	Outcomes Comparison Between Baerveldt 350 and Ahmed ClearPath 250 Tube Shunts for the Treatment of Glaucoma
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Statistical Analysis Plan

1) Roles and Software

All analyses will be performed by the same statisticians from the University at Buffalo Biostatistics, Epidemiology, and Research Design (BERD) team using validated code in R (v≥4.0) and/or Stata/SAS. Two-sided $\alpha=0.05$ unless otherwise noted. Versioned scripts and output will be archived.

2) Study Design Summary

Prospective randomized comparative study of eyes undergoing implantation with either Baerveldt 350 mm² (B350) or Ahmed ClearPath 250 mm² (AC250). Unit of analysis is the eye..

3) Analysis Populations

- **Intention-to-Treat (ITT, primary):** All randomized eyes analyzed by assigned tube shunt implant, regardless of protocol deviations, reoperations, or adjunctive procedures; follow-up contributes until censoring rules apply.

- **Per-Protocol (PP, sensitivity):** Eyes without major protocol deviations and with tube shunt implant received as assigned.
- **Safety Set:** All eyes that underwent study tube shunt implantation.

4) Time Points and Visit Windows

Outcomes summarized at postoperative time points: Day 1 (optional), Week 1, Month 1, Month 3, Month 6, Month 12 and Month 24. Each time point as noted above was specified with a specific window. If multiple observations fall within a window, use the one closest to the nominal time; ties favor the later date.

5) Endpoints & Definitions

Primary Outcome

- **Success** through 24 months, defined at each visit as meeting all the following:
    - IOP **< 21mmHg** and **≥20%** reduction from baseline with/without glaucoma medications
    - No additional glaucoma surgery (slit lamp and in-office procedures are allowed)
    - No loss of light perception vision, endophthalmitis, or any complication requiring additional surgery.
      Success must be confirmed on **two consecutive** visits; failures are persistent thereafter.

Key Secondary Outcomes

- Mean IOP (mmHg) reduction at each time point up to 24 months.
- Mean number of IOP-lowering medications at each time point.
- Cumulative complication rates up to 24 months (overall and by type).
- Mean best-corrected visual acuity (VA) in logMAR at each time point.
- **Time-to-first success** and **time-to-first failure**.
- Cox regression for predictors of success and of failure.
- Baseline comparability between treatment groups.

Baseline Covariates

Age, sex, eye (OD/OS), glaucoma diagnosis, baseline IOP, baseline VA (logMAR), prior ocular surgeries, lens status, race/ethnicity (if collected), number of IOP medications, and center/surgeon (if applicable).

6) General Principles

- **Clustering by person:** Because an individual may contribute two eyes, longitudinal and survival models will use robust (sandwich) standard errors clustered by patient ID or random effects; sensitivity analyses will repeat models after randomly selecting one eye per person.

- **Distributional choices:** Continuous outcomes assessed for normality; if markedly non-normal, use transformations or nonparametric alternatives as specified. Counts may use Poisson/negative binomial as appropriate.
- **Multiplicity:** Primary endpoint tested once at $\alpha=0.05$. Secondary endpoints are exploratory; where families of hypotheses are reported (e.g., multiple time-point comparisons), adjusted p-values (Holm) and 95% CIs will be provided alongside unadjusted results.
- **Missing data:** Mixed-effects models fit under MAR. For survival outcomes, right-censoring at last contact is assumed non-informative. Sensitivity analyses with multiple imputation (m=20) will be performed if >10% outcome data are missing at a key visit.

7) Descriptive and Baseline Comparisons

- Continuous variables: mean±SD (or median [IQR]); between-group comparisons via t-test or Wilcoxon as appropriate.
- Categorical variables: n (%); χ^2 or Fisher's exact test.
- **Standardized mean differences (SMDs)** reported to assess balance; SMD≤0.10 considered well balanced. No formal hypothesis test is required for baseline similarity, but imbalanced covariates may be included in adjusted models.

8) Primary Efficacy Analyses

8.1 Procedures for IOP Success Analysis

- **Visit-specific success proportions:** At each postoperative time point up to 24 months, estimate success proportion per group with 95% CIs; compare groups using generalized estimating equations (GEE) with logit link, exchangeable correlation by person, and robust SEs. Report odds ratios (ORs) and p-values.
- **Time-to-first success:** Kaplan–Meier curves by group; log-rank test for unadjusted comparison. Cox proportional hazards models (device as main predictor) will estimate hazard ratio (HR) with 95% CI. Robust variance will cluster by patient. Proportional hazards (PH) checked via Schoenfeld residuals; if violated, report time-varying HR (interaction with log time) or stratified Cox.
- **Adjusted models:** Multivariable GEE (visit-specific) and Cox models will adjust for pre-specified covariates: baseline IOP, diagnosis, prior surgery, age and baseline medications.

8.2 Time-to-first Failure

- Failure is defined as IOP > 21 mm Hg or less than 20% reduction below baseline on 2 consecutive follow-up visits after 3 months, IOP ,â§ 5 mm Hg on 2 consecutive follow-up visits after 3 months, reoperation for glaucoma, or loss of light perception vision.
- Kaplan–Meier and Cox analyses as above (device main effect; robust SEs; PH checks). Present cumulative failure at 6, 12, 18, 24 months with 95% CIs.

9) Secondary Efficacy Analyses

9.1 Mean Post-Op IOP Over Time

- **Primary longitudinal model:** Linear mixed-effects model (LMM) with random intercept for person (and optionally eye), fixed effects for device, time (categorical), and device×time interaction; adjust for baseline IOP and pre-specified covariates.
- **Pointwise comparisons:** For ClinicalTrials.gov reporting, provide mean±SE at each time point per group and adjusted between-group contrasts with p-values from the LMM (or t-test/Wilcoxon if using cross-sectional summaries only).

9.2 Mean Number of IOP-Lowering Medications

- Analyze using LMM (if approximately normal) or mixed-effects negative binomial regression for counts. Same fixed/random effects and device×time interaction as above. Report means (or adjusted means) with 95% CIs per time point and between-group p-values.

9.3 Visual Acuity (logMAR)

- LMM as in 9.1 with baseline logMAR adjustment. If ceiling/floor or non-normal residuals, consider robust regression or rank-based mixed models; report adjusted mean differences by time.

9.4 Cumulative Complication Rates

- **Any complication:** Cumulative incidence estimated with Kaplan–Meier (time to first complication) and compared by log-rank.
- **By type:** If death or non-glaucoma ocular surgeries are competing risks for some complications, use Fine–Gray subdistribution hazards; otherwise, report proportion with 95% CIs by 24 months and compare with GEE (logit link) across visits.
- **Event rates:** Also report incidence rates per 100 eye-months with Poisson exact CIs; between-group rate ratio via Poisson/negative binomial regression with offset for follow-up time.

9.5 Predictors of Success and Failure (Cox Regression)

- Separate multivariable Cox models for success and for failure including device, age, sex, baseline IOP, diagnosis, prior surgeries, baseline meds, lens status, and center/surgeon as fixed effects. Use robust SEs clustered by patient. Assess PH and functional form (restricted cubic splines for continuous covariates when indicated). Report adjusted HRs with 95% CIs.

10) Handling Reoperations and Additional Interventions

- **For longitudinal means:** Post-reoperation IOP, VA, and medication data remain in ITT analyses but will be flagged; sensitivity analyses will censor at reoperation date and re-fit primary longitudinal and survival models.
- **For success/failure endpoints:** Reoperation for glaucoma constitutes immediate failure (per definition above).

11) Outliers, Protocol Deviations, and Data Quality

- Extreme values will be verified against source data; analyses will be performed with and without outliers for sensitivity if they materially affect results. Major protocol deviations are documented; PP analysis excludes these eyes and is reported alongside ITT.

12) Interim Analyses and Data Monitoring

No formal interim efficacy analyses are planned. Safety will be summarized periodically but without hypothesis testing.

13) Presentation of Results

ClinicalTrials.gov–compatible tables will include:

- Baseline characteristics (means/SDs or n/% with SMDs).
- Visit-wise means (IOP, meds, VA) by group with adjusted between-group differences and p-values.
- Success/failure KM curves with numbers at risk and HRs (95% CI).
- Cumulative complication summaries (overall and by type).
- Multivariable model outputs (betas/HRs, 95% CIs, p-values).
- Pre-specified sensitivity and subgroup analyses.