REAGIR

Rose Bengal Electromagnetic Activation with Green light for Infection Reduction

Statistical Analysis Plan

1. Administrative Information

Trial registration:	NCT05110001
Funder:	Funder: National Eye Institute (grant # UG1 EY028518)
SAP Version:	Version 7, Updated 03 December 2024 A revision history for this document is included at the end.
Protocol Version:	Refers to Protocol Version 6
Contributors:	Statisticians responsible: Benjamin F. Arnold[1] and Travis C. Porco[1] Principal Investigators: Thomas M. Lietman[1] and Jennifer Rose-Nussbaumer[1,2]

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SAP Table of Contents

This SAP was organized following guidelines proposed in:

Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. *JAMA*. 2017;318: 2337–2343. PMID: 29260229

The companion computational notebook with underlying sample size calculations presented herein is entitled: `REAGIR-sample-size-power.Rmd / .html`; it is saved in the same directory as this document.

2. Introduction

2.1. Background and rationale

The trial's protocol includes detailed background and rationale. This trial is being conducted in coordination with the Steroids and Cross-linking for Ulcer Treatment (SCUT II) trial. Briefly, the best treatment strategies for fungal keratitis have not been well characterized. Topical natamycin, a polyene, is the only antifungal agent approved by the Food and Drug Administration (FDA) for treatment of fungal keratitis. Although much less common, acanthamoeba keratitis (AK) may have the most prolonged and severe course of any corneal infection. AK is typically related to contact lens use and the incidence of these infections varies from as low as 1% to 4-8% of culture positive microbial keratitis cases.

Recently a crosslinking method has been proposed that uses rose bengal (RB) as the photosensitizer and green light (532 nm) and is termed RB-PDT. RB-PDT appears to have similar effects on corneal biomechanical properties, is safe for limbal stem cells and endothelium, and demonstrates less toxicity to keratocytes in vitro than corneal cross-linking with riboflavin (the focus of the SCUT II trial). In vitro RB-PDT appears to be effective against fungal and acanthamoeba isolates.

This trial will assess whether cross linking with rose bengal photodynamic therapy (RB-PDT) is a beneficial adjuvant in the treatment of fungal, acanthamoeba, and smear or culture negative corneal ulcers.

2.2. Objectives

Specific Aim: To determine if cross linking with rose bengal (RB-PDT) is a beneficial adjuvant in the treatment of fungal, acanthamoeba, and smear or culture negative corneal ulcers.

We hypothesize that there will be improved visual acuity at 6 months among those randomized to adjuvant RB-PDT after controlling for baseline visual acuity.

We anticipate that there will be smaller infiltrate/scar size and decreased rate of perforation and/or need for therapeutic penetrating keratoplasty (TPK) at 6 months among RB-PDT treated patients.

3. Study Methods

3.1. Trial design

REAGIR is a multi-site, individually randomized, placebo-controlled trial. Patients presenting to one of the Aravind Eye Hospitals in Indiaor to the University of California, San Francisco (UCSF) will be eligible for inclusion if they meet eligibility criteria (SAP section 5.2).

Enrolled participants will be randomized with equal probability (1:1) to one of two groups:

- **Sham RB-PDT**: Chlorhexidine gluconate, 0.02% (acanthamoeba), moxifloxacin 0.5% (smear/culture negative) or natamycin 5% (fungal keratitis) plus sham RB-PDT

- **RB-PDT**: Chlorhexidine gluconate, 0.02% (acanthamoeba), moxifloxacin 0.5% (smear/culture negative) or natamycin 5% (fungal keratitis) plus RB-PDT

Study participants will be required to have 8 visits: enrollment/baseline (Day 0), Day 1 (visit window: Day 1 or Day 2) for further assessments and to begin study drug, Day 2 for the cross-linking procedure within 48 hours of enrollment, and follow-up visits at 3 days, 3 weeks (visit window: 2.5 – 5 weeks), 3 months (visit window: 2.5 -3.5 months), 6 months (visit window: 5-7 months) and 12 months (visit window: 10-14 months). Additional visits may be needed and will be determined by the physician/investigator.

3.2. Randomization

Randomization will be stratified by site. Stratified, block randomization will ensure that an approximately equal number of patients are randomized to each treatment group by site. The exact block size will be randomly permuted (e.g., block size of 4 with probability 0.7 and 6 with probability 0.3) with block sizes and their probabilities known only to the biostatistician.

Once an eye is in the study enrolled (only one eye can be enrolled from each patient), the study coordinator will assign the study participant's eye an ID (alpha-numeric code) and organize the procedure in the operating room within 48 hours of enrollment. Once the study participant has been assigned a study participant ID and randomized to treatment arm, they will be included in the intent to treat analysis.

3.3. Sample size

The trial's sample size calculation was based on the primary outcome, 6-month BSCVA. We informed the calculation with measurements from the first Steroids for Corneal Ulcers Trial (SCUT), among patients enrolled with between 20/60 and 20/400 vision. The SCUT trial measured BSCVA at baseline, 3-months, and 12-months. We conservatively used the 12-month outcome measure for the calculations since there was no 6-month measurement. The standard deviation of BSCVA at 12 months was 0.293. Since the primary analysis will adjust for baseline BSCVA, we used an estimate of the residual standard deviation, which is $SD_r = SD\sqrt{1-r^2}$, where *r* is the correlation between the baseline measure and primary endpoint. In SCUT, the correlation between baseline and 12-month BSCVA among patients with between 20/60 and 20/400 vision at enrollment was 0.216. We thus assumed a residual standard deviation of $0.293\sqrt{1-0.216^2} = 0.286$.

Assuming a significance level of 0.05, allowing for approximately 15% loss to follow up, we estimate that we will have 90% power to detect a 1.1-line difference (logMAR 0.11) between groups with 165 study participants per arm (330 total). For the same sample size and under the same assumptions, the detectable difference at 80% power is 1.0-lines (logMAR 0.10). These calculations were based on the standard power formula for the T-test (using an estimated residual standard deviation).

3.4. Statistical framework

The trial will use a superiority test of the hypothesis that patients who receive the RB-PDT adjuvant will have better BSCVA outcomes compared with patients who receive sham RB-PDT. The analysis will be intention-to-treat (ITT), with all patients analyzed according to their randomized allocation.

3.5. Statistical interim analyses and stopping guidance

The Data and Safety Monitoring Committee will meet to review the interim efficacy data when primary outcome data is available on 100 study subjects (approximately 1/3 of the 330 target enrollment).

The DSMC will make one of the following recommendations:
• Continue the trial without modifications
• Continue the trial with study modifications
• Terminate enrollment or treatment in the trial because of efficacy
• Terminate enrollment or treatment in the trial because of futility
• Terminate enrollment or treatment in the trial because of safety concerns

The DSMC will determine the database closure dates for each report in advance; archival copies of the (a) main SQL database, and (b) study analysis file as they exist at the time of each report will be maintained. All reports will be sent using secure email to the members of the DSMC two weeks prior to each meeting.

The DSMC will make decisions with the benefit of pre-specified decision guidelines. These guidelines were agreed upon at the initial meeting, and take into consideration (a) safety, (b) efficacy, (c) clinical importance, and (d) validity.

Efficacy. An unmasked interim analysis will be conducted when 100 participants (approximately 1/3) reach the primary endpoint to determine whether or not sufficient evidence has accumulated to justify stopping the trial because one treatment is clearly superior (and therefore should be extended to all future cases). The guidelines for efficacy will use group sequential boundaries for judging the statistical significance of the primary outcome measure. We propose to use a Lan-DeMets flexible alpha spending approach, with $\alpha^*(t^*)= \alpha\ (t^*)^{\Theta}$, where $\theta= 3.02$ (chosen so that the two-sided *P*-value to stop the trial for efficacy is 0.0005) [1]. The interim analysis for efficacy as well as for futility will be conducted with equal weight for each of the two contrasts. This boundary corresponds to an effect size of 1.8 lines (0.18 logMAR).

Futility. Early discontinuation due to the unlikeliness of significant findings conditional on interim results may be considered, based on the original sample size considerations. For evaluating futility, we propose discontinuation for futility if the conditional power to detect a one line *benefit* drops below 20% at the interim analysis [2]. Conditional power will be derived by simulation of the unobserved future patients according to the original alternative hypothesis. Our proposed futility guidance is one-sided, and is subordinate to efficacy analyses.

Harm. Stopping for harm will be done at the judgment of the DSMC. Several endpoints will be examined, including (a) the best spectacle-corrected visual acuity at six months, (b) adverse events, and especially (c) serious adverse events, including corneal perforation or mortality. While the analysis would consider unbalanced distribution of predictive factors such as (a) infiltrate/scar size at presentation, (b) organism, and (c) repeat culture status, it is recognized that ethical considerations require careful considerations of statistical tests as well as qualitative judgments in the light of experience.

All subjects who provide informed consent will be accounted for in this study. We will present the number lost to follow-up and the number of protocol deviations by arm. The proportion of

subjects reporting adverse events and serious adverse events will be reported by arm to the DSMC and will be compared using a Fisher's Exact Test.

3.6. Timing of the final analysis

The primary analysis will commence after all enrolled patients complete their 6-month outcome assessment (or would have completed their 6-month assessment, if lost to follow-up).

3.7. Timing of outcome assessments

Protocol section 1.3 includes a detailed measurement schedule for the trial. Participant BSCVA will be measured at enrollment, and at 3-months, 6-months, and 12-months following treatment. The 6-month measurement is the primary outcome. Measurements at 3-months and 12-months are secondary outcomes.

4. Statistical Principles

4.1. Confidence intervals and *P*-values

We will test for difference between arms in the primary outcome (BSCVA at 6 months follow-up) using a p=0.05 level to assess statistical significance. We will construct two-sided 95% confidence intervals to test for superiority of RB-PDT versus sham.

We will report 95% confidence intervals on our measures of effect (difference in BSCVA logMAR) on each secondary outcome. We do not plan to adjust secondary outcome confidence intervals for multiplicity because we expect them to be highly correlated and together they provide corroborating evidence for or against the primary outcome hypothesis.[3]

4.2. Protocol deviations

The analysis population will be intention to treat, and will include all participants enrolled and randomized. Adherence to protocol will be assessed in the hospital for the first 3 days with observed administration of the treatment. Later compliance will be assessed by questioning the patient and collecting empty bottles over the entire treatment duration. The trial will assess whether patients adhered to the treatment regimen: Chlorhexidine gluconate, 0.02% (acanthamoeba), moxifloxacin 0.5% (smear/culture negative) or natamycin 5% (fungal keratitis), plus RB-PDT or sham RB-PDT depending on the group. Patients who deviate from protocol will be included according to randomized group in the intention-to-treat analysis.

5. Trial Population

5.1. Screening data

We will report the number of patients screened by study side and characteristics to the extent they are available to assess representativeness of the enrolled study population.

5.2. Eligibility

Participants who are screened will be eligible to enroll in the trial if they meet these criteria:

- either smear or culture positive fungal, or
- acanthamoeba keratitis, or
- smear and culture negative corneal ulcers and moderate to severe vision loss, defined as Snellen visual acuity of 20/40 or worse

5.3. Recruitment

The trial will report the number of participants screened, eligible to enroll, randomized, and measured at each trial visit (Protocol section 1.3 includes details about each planned visit). The trial will report recruitment progress at regular DSMC meetings to monitor trial progress.

5.4. Withdrawal/follow-up

We will report the number and proportion of patients in both study arms who withdraw from the trial, along with reasons. We will report this information in the trial's CONSORT flow chart, summarizing losses to follow-up at each trial visit (3 months, 6 months, 12 months). The analysis will be intention-to-treat: patients will be analyzed according to the arm they are randomized.

5.5. Baseline patient characteristics

We will summarize trial participant age, sex, occupation, medication use at enrollment, eye trauma, and clinical characteristics at enrollment, including medication use at enrollment, trauma, affected eye, visual acuity, infiltrate and/or scar size, hypopyon, depth, epithelial defect, duration of symptoms, and systemic disease. We will summarize means (or proportions for binary variables) by treatment group, along with standard deviations for quantitative variables.

6. Analysis

6.1. Outcome definitions

Primary Outcome:
Best spectacle-corrected visual acuity measured in logMAR, 6 month follow-up visit

Secondary Outcomes:

- Microbiological cure on repeat smear and culture at Day 2
- Interaction of minimum inhibitory concentration (MIC) and CXL on best spectacle-corrected visual acuity
- Infiltrate/scar size/depth, as measured by clinical exam, clinical photographs, Pentacam and OCT at week 3 and months 3, 6, and 12
- Adverse events including rate of perforation/need for TPK
- BSCVA at Day 1, 3 weeks, 3 months, and 12 months
- Astigmatism, higher order aberrations, topography, and densitometry as measured on Pentacam at week 3 and months 3, 6, and 12
- Corneal thickness and scar size/depth as measured by AS-OCT at week 3 and months 3, 6, and 12
- Basal nerve plexus, white blood cell count, and keratocyte density on confocal microscopy at week 3 and months 3, 6, and 12

- Visual function questionnaire (VFQ) will be compared between groups at 6 months, controlling for Day 1 VFQ
- Pain scale at baseline, Day 1, and Day 3
- Subgroup analysis of study participants receiving prior topical antimicrobial therapy

6.2. Analysis methods

Primary Outcome

Visual Acuity at 6 months. We will use a multiple linear regression model to estimate the mean difference between groups in BSCVA measured in logMAR at 6 months. The model will include covariates for treatment arm (a binary indicator variable for RB-PDT), indicators for study site (randomization strata), and baseline pinhole visual acuity. We propose a two-sided alpha of 0.05 for the primary analysis.

For study participants who experience perforation or the need for TPK this will be noted and BSCVA will be recorded prior to performing surgery (either corneal glue or TPK). These study participants actual 6-month visual acuity will be used in the primary analysis. As a sensitivity analysis, the last observation (at 3 weeks or 3 months) will be carried forward (LOCF) as the 6-month BSCVA.

The measurement window for the 6-month primary BSCVA outcome will be 5-9 months. The window was chosen after examining the distribution of measurement timing in masked data. As a sensitivity analysis, we will include all participants, including those who had their primary outcome measured out-of-window.

A supplementary analysis using linear mixed effects regression will be conducted to analyze all BSCVA data (including 3-week and 3-month observations). The model will include baseline BSCVA and treatment assignment as covariates (fixed effects) plus a random effect for patient to allow for repeated measures over time. Such analyses will be sharply distinguished from the primary pre-specified analysis. Permutation testing will be the basis of inference. Specifically, we will conduct 10,000 random permutations of treatment assignment, and conduct the primary regression analysis on these re-randomized data sets. We will then compare the observed regression coefficients to the randomization distribution, reporting the quantiles.

In all analyses, model adequacy will be checked by examination of residuals or other goodness of fit tests as needed. Inadequate model fit will prompt us to report alternative models. If there are chance imbalances in prognostic baseline patient characteristics, a secondary analysis will include them as covariates in the regression model.

Secondary Outcomes

Visual Acuity at 3 weeks, 3 months, and 12 months. We will compare BSCVA between arms at 3 weeks, 3 months, and 12 months follow-up using the same approach as the primary analysis. We will only complete this analysis after the primary analysis is complete and the trial is unmasked.

Scar/infiltrate**.** The analysis for scar/infiltrate size will follow the templates for visual acuity given

above. Multiple linear regression models will be used to evaluate 3-week, 3-month, 6-month, and 12-month scar size by treatment arm while correcting for baseline measurements. Corneal thinning and scarring will be evaluated similarly using Anterior Segment Optical Coherence Tomography (AS-OCT) correcting for baseline values.

Corneal Perforation**.** A Cox proportional hazards model will estimate the hazard of perforation, defined as perforation (flat anterior chamber with presence of iris plugging a defect in the cornea or seidel positivity) or the need for TPK while correcting for baseline infiltrate depth.

Microbiological cure. We will re-culture all study participants at Day 2, prior to starting antibiotics to assess the effect of RB-PDT on rate of microbiological cure. We hypothesize that those in the RB-PDT group (Arm 2) will have a higher rate of microbiological cure on 2 day cultures than those randomized to the Sham group (Arm 1).

We propose the primary analysis to be a Fisher's exact test comparing the proportion of positivity at follow-up between initially culture positive individuals who were assigned to RB-PDT (Arm 1) versus initially culture positive individuals assigned to the Sham group (Arm 1). Additionally, we will report the results for initially culture negative individuals as a supplementary analysis in a linear binomial regression with assignment, indicators for site (randomization strata), and initial culture results as covariates.

Visual Function Questionnaire (VFQ). VFQ will be compared between arms controlling for Day 1 VFQ. NEI-VFQ in the US and the Indian-VFQ (IND-VFQ) in India. This will be conducted using linear regression with baseline and treatment assignment variables.

Pain Scale. Pain is assessed at day 0, day 1, and day 3 using a 0-10 scale for patient self-assessment. Multiple linear regression models will used to evaluate 3-day pain by treatment arm while correcting for baseline pain.

Minimum Inhibitory Concentration (MIC). The analysis of MIC will follow the primary analysis but include an interaction of minimum inhibitory concentration (MIC) and RB-PDT on best spectacle-corrected visual acuity.

Pre-specified Subgroup Analyses
The trial has two planned subgroup analyses. The first subgroup analysis will stratify the analysis by infectious organism: fungal, acanthamoeba, or smear and culture negative. If patients are smear negative and are suspected fungal or acanthamoeba, we will use confocal microscopy to determine the patient's subgroup. The second subgroup analysis will stratify patients by whether they had received prior topical anti-microbial therapy at enrollment. In both cases, we will add indicator variables for subgroups to the linear regression model plus interaction terms between indicator variables and the treatment arm. We will test for interaction on the additive scale based on coefficients on the interaction terms in the models. Ulcer depth is thought to be a strong determinant of outcomes among patients with acanthamoeba infections. The infectious organism subgroup analysis will include ulcer depth as an additional covariate in the model to potentially improve precision.

6.3. Missing data

If outcome data are missing for >15% of participants we will report results from sensitivity analyses for missing data [4,5]. We selected 15% missing because trials with >20% missing values are thought to be a concern for bias [6]. The primary analysis will assume outcomes are

missing completely at random. We will relax this assumption slightly, assuming that outcomes are missing at random (MAR) with an inverse-probability weighted (IPW) estimator. We will model the probability of censoring as a function of baseline patient characteristics with a logistic regression model, and will use the inverse of the predicted probabilities from the model to re-weight the analysis population to reflect the full study population at the time of enrollment, using a doubly-robust targeted maximum likelihood estimator that also includes an outcome model using the same covariates [7]. Baseline characteristics used in the censoring model will include treatment arm, site, age, sex, occupation, medication use at enrollment, eye trauma, ocular measures at enrollment (infiltrate and/or scar size, depth, epithelial defect size, duration of symptoms, BSCVA). We will additionally consider a range of scenarios assuming the outcomes are missing not at random (MNAR), *i.e.* systematically, using a pattern mixture model approach described by Little et al. [4], whereby we model BSCVA with a linear model as a function of covariates listed for the IPW estimator; missing outcomes will then be imputed using the model fit to predict, adding a shift parameter, Δ, that we vary across a range of values.

6.4. Additional analyses

We plan to complete the following exploratory analyses.

Imaging Outcomes. To be analyzed by a **masked grader** in the **Proctor Reading Center (PRC)**. We propose five different analyses, based on imaging at baseline, 3 weeks, 3 months, 6 months and 12 months.

- *Confocal Microscopy.* An *in vivo* microscope, which allows examination of the cornea at the cellular level. Outcomes include quantitative estimates of the infectious organism (if visualized on confocal), basal nerve plexus density, white blood cell and keratocyte density in the cornea (these are continuous outcome variables). (based on the Heidelberg Retina Romograph II, Rostock Cornea Module (RCM; Heidelberg Engineering, GmBH, Gernany).
    - *Corneal nerves:* Will be analyzed with *ACCMetrics*, an automated corneal nerve fiber analyzer with output variables such as corneal nerve fiber density, branch density, fiber length.
    - *White blood cell/keratocyte density:* Manual quantitative analysis of epithelial cells, inflammatory cells and keratocytes will be performed by a masked grader at the PRC. Stromal depth for the demarcation line and RB-PDT-induced photo-oxidative damage will also be assessed.
    - *Statistical analysis:* We propose to conduct linear mixed effects regression using treatment assignment and baseline values as covariates, using the same template as we did for BSCVA. The most important analysis will be for contrasting the RB-PDT versus RB-PDT sham groups, though we will also examine the effects of steroids. We note that changes over time are possible, and so an interaction with time will be included. This is a secondary analysis.
- *Pentacam Scheimpflug Tomography*. Is a rotating scheimpflug camera, which provides 3 dimensional images of the cornea. In addition to topographic maps with keratometric readings of the anterior and posterior cornea, Pentacam reports on the total corneal power, corneal thickness maps, higher order aberrations and densitometry.
    - *Astigmatism:* comparing steep and flat Ks and total astigmatism in diopters between groups controlling for baseline measurements
    - *Higher order aberrations:* comparing the quantitative measure of irregular astigmatism, expressed in microns as the root mean square (RMS) of the

Zernike polynomials across the pupil (approximately central 4 mm of the pupil) controlling for baseline measurements
    - *Densitometry:* comparing a measure of corneal reflectance (i.e. scarring) in gray scale units controlling for baseline measurements
    - *Statistical analysis*: will be similar to that describe above, linear mixed effects regression using treatment assignment and baseline values as covariates, using the same template as for BSCVA.
    - For a final supplementary analysis, we will also repeat the BSCVA analyses, but now including Pentacam densitometry at baseline as a predictor. We will report both the regression coefficient for baseline densitometry as a predictor, as well as the coefficient for treatment.
- *High-resolution Anterior-Segment-Optical Coherence Tomography.* Provides high-resolution cross-sectional images of the cornea.
    - *Corneal thickness:* masked grader will identify central corneal thickness and point of maximal thinning using the calipers on the OCT machine in microns.
    - *Infiltrate/scar size and depth:* as measured by masked grader with the calipers on the OCT machine in millimeters.
    - *Statistical analysis:* Multiple linear regression models will be used to evaluate 3-month, 6-month, and 12-month scar size by treatment arm while correcting for baseline measurements. Corneal thinning and scarring will be evaluated similarly using Anterior Segment Optical Coherence Tomography (AS-OCT) correcting for baseline values.

6.5. Harms

All adverse events will be tabulated and reported. Statistical comparisons will be conducted using Fisher's exact test, but with the caution that failure to find a statistically significant difference cannot be used to infer a lack of risk difference, since the study is not powered to examine rare outcomes. Procedures for reporting both adverse events and serious adverse events, including notification of the Medical Monitor, will be reviewed by the DSMC prior to opening enrollment. We will categorize adverse events, severe adverse events and events of interest following recommended best practices for clinical trial monitoring and reporting [8].

SAP Section 3.5 (Interim analyses) includes additional discussion regarding harms and stopping guidance.

6.6. Statistical software

The team will conduct data processing and analyses with R statistical software (v 4.3 +).

7. References

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8. Revision history

Version	Date	Summary of Changes, Justification, and Timing vis-à-vis key trial events (enrollment completion, interim analyses, unmasking, etc)
1	2020-07-16	• First draft of the statistical analysis plan
2	2021-11-17	• Added Clinical Trials registration number (NCT) • Removed Kaiser Permanente • Updated Dr. Rose-Nussbaumer's affiliation to Stanford
3	2023-05-08	• Updated secondary outcomes based on Protocol secondary outcomes
5	2023-08-29	• Added to subgroup analyses confocal microscopy if fungal or acanthamoeba smear is negative
6	2024-04-12	• Added in-window range of primary analysis to Section 6.2
7	2024-12-03	• Primary analysis will not do LOCF for CP/TPK but instead use actual 6-month value (Section 6.2). Specified analyses for secondary outcomes (Section 6.2).