SOP 31: Analysis plan

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SOP Chronology			
Version	**Date**	**Reason for Change**	**Author / Review**
V1.1	13/06/2025	Review and update ahead of final locking of analysis plan	Sandip Das Matthew Burton David Macleod
V1.2	28/08/2025	Review and update of analysis plan	Sandip Das Matthew Burton David Macleod
V1.3	14/01/2026	Review and final locking of analysis plan before starting analysis.	Sandip Das Matthew Burton David Macleod

Purpose
This SOP describes the trial analysis plan.

Trial Synopsis
This is a prospective, single-masked, parallel group, two-arm cluster randomised controlled trial with 40 clusters (20 per arm). We will test the hypothesis that a complex intervention package can reduce blindness from severe MK. The intervention package will include tools for early recognition, prompt chlorhexidine 0.2% treatment and rapid referral of MK. The study participants will be individuals presenting to PHCs with corneal abrasions or corneal infections (MK), who meet eligibility criteria. At baseline presentation in the primary health centres the health worker will take a history, perform a simple examination of the front of the affected eye and initiate treatment. Patients will be referred to the regional eye unit for assessment and ongoing treatment. The primary outcome will be the proportion of known MK cases, by arm, which have a best spectacle BSCVA of worse than 3/60 (WHO blindness definition) at three months. This will be measured by a trial-certified optometrist, independent of all other aspects of the study and masked to the allocation.

Trial Objectives

Primary Objective
To determine if a complex intervention package delivered at the Primary Health Centres, including early recognition, prompt chlorhexidine 0.2% treatment and rapid referral can result in reduced rates of blindness from severe MK at three months, compared to the standard of care.

Secondary Objectives
To determine whether there is a difference between the complex intervention pack at PHCs and the control standard of care in terms of secondary outcomes:

1. BSCVA at 3 months by a trial certified optometrist
2. Scar/infiltrate size at 3 months, slit lamp examination by ophthalmologists (trial certified).
3. Perforation and / or therapeutic corneal transplant (TPK) by three months, slit lamp examination by ophthalmologists.
4. Diagnostic accuracy in primary care
5. Time between symptom onset and presenting to primary care facility
6. Adherence to and time taken to attend referral at eye hospital
7. Quality of life questionnaires: EQ-5D, WHO/PBD-VF20, WHOQOL-BREF
8. Cost effectiveness analysis

Trial Design
Cluster randomised controlled trial.

Study Population and Clusters
This trial will be conducted within the Siraha district of province 2, Nepal. Siraha district has 112 health post and PHCs with each serving an average population of 5,000 people. Our target population size per cluster is 10,000 people. Therefore, we will probably need to combine two neighbouring health centres to form a single cluster unit with a total catchment population of 10,000 people. These 112 Health posts and PHCs units will be randomised to the two arms. We shall allow for a “buffer zone” between the intervention and control arm facilities to minimise cross contamination. However, because village boundaries in Nepal are not well demarcated, participants will be considered as per the arm they present to regardless of their residential address arm. For example, if a participant from the “control arm” village opts to present at a facility in the “intervention arm”, they will be considered as per the facility and vice versa. The main referral eye hospital shall be at Sagarmatha Choudhary Eye Hospital (SCEH), Lahan, Nepal.

Clusters will be comprised of primary health centres (PHC) and their catchment populations (typically around 10,000 people). The cluster PHCs will be randomised to either standard practice or the new complex intervention package for managing MK in the primary care setting.

Randomisation
A list of participating health centres (clusters) will be compiled; these will be the unit of randomisation. The travel time from the health centre and direction to the central eye unit will be determined. Health centres will be randomly

allocated, in a 1:1 ratio, to each arm using restricted randomisation on distance to the eye unit, to minimize imbalance between arms. This will be done by an independent statistician. See SOP29 for additional details.

Masking

It is not possible to mask the health workers in the health centre and the participants themselves to the arm. The ophthalmologists responsible for the clinical assessment will be masked to the intervention arm. Masked independent grading of photographs will be done centrally to confirm the outcome measures and assess for any systematic bias in the clinical assessments. The primary outcome, BSCVA, will be assessed at three months by a masked optometrist.

Outcome Measures

Primary Outcome Measure:

The primary outcome will be the proportion of known MK cases, by arm, that have a BSCVA of worse than 3/60 (WHO blindness definition) at three months, in the affected eye. This will be measured by a trial-certified optometrist, independent of all other aspects of the study and masked to the allocation.

Secondary Outcome Measures:

1. BSCVA at 3 months by a trial certified optometrist
2. Scar/infiltrate size at 3 months, slit lamp examination by ophthalmologists (trial certified).
3. Perforation and/or Conjunctival flaps and/or therapeutic corneal transplant (TPK) by three months, slit lamp examination by ophthalmologists.
4. Diagnostic accuracy in primary care
5. Time between symptom onset and presenting to primary care facility
6. Adherence to and time taken to attend referral at eye hospital
7. Quality of life questionnaires: EQ-5D, WHO/PBD-VF20, WHOQOL-BREF
8. Cost effectiveness analysis

Sample Size

Primary analysis of primary outcome will be a test for superiority. Typically, >60% of MK have final vision worse than 3/60 (Blind). A sample of 40 health centres (20 per arm) would have 90% power and 95% confidence to detect a reduction from 60% to 30% in the proportion of blinding infections (visual acuity worse than 3/60) in intervention compared to control arm.

Assumptions:

- coefficient of variation (k) 0.25
- 10 MK cases/health-centre/year (based on incidence of 100/100,000/year)
- health centre catchment population 5,000.
- The trial will run for at least one year.

Statistical Analysis Plan

CONSORT guidelines for analysing and reporting cluster randomised controlled trials will be followed. All analysis will be done using Stata. All analyses will be by intention-to-treat: i.e. all clusters will be analysed according to their original randomisation regardless of coverage or other variables.

Interim Analyses
No interim analyses on the primary outcome will be carried out.

Demographic and presenting clinical characteristics
Cluster-level, trial arm-level and overall demographic characteristics will be presented using descriptive statistics. Separate presentation for people presenting to the PHCs and at SCEH.

People presenting at the PHCs:

1. Number of clusters
2. Mean/median cluster population (estimated for health service data, based on 2021 census)
3. Age (mean, median, range, age-group categories)
4. Sex, female n/N (%)
5. Total number of patients presented for eye evaluation.
6. Diagnosed with an abrasion n/N (%)
7. Diagnosed with MK n/N (%)
8. Number of people referred with presumed MK to SCEH

People referred to and attending SCEH:

1. Number of clusters that referred cases
2. Age (mean, median, range, age-group categories)
3. Sex, female n/N (%)
4. Occupation
5. Literacy
6. MK cases attended SCEH (n, %)
7. Other diagnoses of referred patients (n, %)
8. Presenting severity – vision, lesion size, and other measures of clinical severity

Assessment of Outcomes

Primary analysis of the primary outcome
Primary analysis will be an individual-level analysis. The primary analysis will be adjusted for *cluster level* covariates included in the restricted randomization (settlement type, direction), to account for any imbalance in the random allocation of clusters to arms. We will also adjust for disease severity, using presenting visual acuity in the affected eye. The analysis will be by intention-to-treat, with participants analysed per the arm to which they were randomised, as determined by the PHC they presented to. The intervention effect will be estimated as an odds ratio and 95% confidence interval, estimated using a random effects logistic regression, including cluster as a random effect.

Secondary analysis of the primary outcome
The prevalence of the primary outcome is expected to be relatively high. Therefore, the odds ratio will not closely approximate to the risk ratio. As risk ratios and risk differences are more interpretable to most readers, we also intend to report the risk ratio and risk difference. Within each cluster the proportion of participants who are blind (BSCVA <3/60) at 90 days will be calculated. The risk difference will be calculated by using the 40 cluster-level proportions and performing linear regression. The risk ratio will be calculated by linear regression using the log of the cluster-level proportion, before back transforming the difference to provide the risk ratio.

Sensitivity analyses of primary analysis
The primary analysis will exclude participants where the outcome is missing. A sensitivity analysis will be performed carrying forward the most recent visual acuity observation taken prior to the 90-day visit. Any patients who have had a corneal graft at any point would be classified as blind.

Analysis of secondary outcomes

Secondary outcomes that are continuous variables will be analysed using mixed-effects linear regression, including cluster as a random effect. Secondary outcomes that are binary variables will be analysed using logistic regression, including cluster as a random effect.

Secondary outcome measure	Analysis details
BSCVA at 3 months by a trial certified optometrist	The BSCVA will be analysed by mixed-effects linear regression, adjusting for baseline BCVA and the factors restricted on including cluster as a random effect
Scar/infiltrate size at 1 week, 3 weeks, and 3 months, determined by slit lamp examination	The size of infiltrate and scar in healed ulcer will be measured at every scheduled follow-up visit. The geometric mean of the two axes measured in mm at 1 week, 3 weeks, and 3 months. The infiltrate/scar sizes at all the visits will be compared between the trial arms. This will be done using a mixed effects linear regression with cluster as a random effect and trial arm as the main exposure. The comparisons between arms will be: 1. Scar/infiltrate size at 3 months, unadjusted 2. Scar/infiltrate size at 3 months, adjusted for size at enrolment (from image analysis) 3. Scar/infiltrate size at enrolment (from image analysis)
Perforation and/or therapeutic corneal transplant (TPK) by three months, determined by slit lamp examination.	Total number of patients who have perforated cornea and/or undergone conjunctival flaps and/or require TPK by 3 months will be reported using CIs and descriptive statistics. As the study is not powered to evaluate the difference in perforation rate or TPK, an exploratory analysis by using random effect logistic regression with perforation/TPK by 90 days as the outcome, cluster as the random effect and trial arm as the main exposure.
Diagnostic accuracy in primary care	The diagnostic category determined by the PHC staff will be compared with the assessment of the images they collected on the same eye, and also where available the diagnostic result from SCEH among those that attended their referral.
Time between symptom onset and presenting to primary care facility	Date of symptom onset will be measured using patient history/questionnaires. The exposure of interest will be trial arm, with the hypothesis that patients in the intervention arm will present sooner to primary care than in the control arm. The analysis will be performed using a Cox regression with time to attendance as the outcome and trial arm as the exposure, adjusted for cluster.
Adherence to and time taken to attend referral at eye hospital	The adherence to the referral to SCEH will be compared between two arms using logistic regression, including cluster as a random effect. The analysis of time taken to attend referral at SCEH will be done using Cox regression, using time to attendance as the outcome and trial arm as the exposure.
Quality of life questionnaires: EQ-5D, WHO/PBD-VF20, WHOQOL-BREF	The mean quality of life score will be compared between arms using a linear regression with quality-of-life score at 90 days as the outcome and trial arm as the exposure. This analysis will be done both unadjusted and adjusted for quality-of-life score at enrolment.
Cost effectiveness analysis	If there is evidence of an effect from the intervention, we will conduct a cost-effectiveness analysis. The direct costs incurred by patients calculated at 3 months follow-up will be compared between the intervention and the control arms using a mixed effects linear regression with cost incurred as the outcome and trial arm as the exposure. Economic cost estimation can also be calculated using the EQ-5D questionnaire which will be asked at baseline and 3 months. The mean overall costs incurred by patients will be compared between arms using t-test for significance. The difference from the baseline and 3 months EQ-5D mean scores will be compared similarly.

Missing data

No data will be imputed.

Adverse Events

All reported adverse events will be reviewed by the trial manager and responsible Ophthalmologist and given a grading of severity and likelihood of relatedness to the trial interventions. The Principal Investigator (PI) will review all serious

adverse events. Timescales will be according to Good Clinical Practice. Descriptive statistics will be provided on the number, nature, severity and relatedness of all reported adverse events, with additional details reported on all serious adverse events. Cluster-level data and age-group data will be presented. The rate of adverse events will be compared between trial arms.