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The Village-Integrated Eye Worker trial (VIEW): rationale and design of a cluster-randomized trial to prevent corneal ulcers in resource-limited settings

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Abstract

Introduction. Corneal opacity is a leading cause of blindness worldwide. In resource-limited settings, untreated traumatic corneal abrasions may result in infection and ultimately, opacity, which can reduce vision. Though antimicrobial treatment of corneal ulcers may successfully cure infections, the scarring that accompanies the resolution of infection can still result in visual impairment. Prevention may be the optimal approach for reducing corneal blindness. Studies have employed community health workers to provide prompt administration of antimicrobials after corneal abrasions to prevent infections, but these studies were not designed to determine the effectiveness of such a program.

Methods and analysis. The Village-Integrated Eye Worker trial (VIEW) is a cluster-randomized trial designed to assess the effectiveness of a community health worker intervention to prevent corneal ulcers. Twenty-four Village Development Committees (VDCs) in Nepal are randomized to receive a corneal ulcer prevention program or to no intervention. Female Community Health Volunteers (FCHVs) in intervention VDCs are trained to diagnose corneal abrasions, provide antimicrobials, and to refer participants when needed. An annual census is conducted over the 3-year study period in all study VDCs to assess the incidence of corneal ulceration via corneal photography (primary outcome). Masked outcome assessors grade corneal photographs to determine the presence or absence of incident corneal opacities. The primary analysis is negative binomial regression to compare the incidence of corneal ulceration by study arm.

Ethics and dissemination. The University of California San Francisco Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council have given ethical approval for the trial. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Registration. This trial was registered at clinicaltrials.gov (NCT01969786) on October 21, 2013.

Strengths and limitations of this study

- VIEW is the first randomized controlled trial designed to determine the effectiveness of a community health worker intervention to prevent corneal ulcers.
- The large simple trial design allows detection of a modest intervention effect for a rare outcome.
- Given the nature of the intervention, the study participants and field staff could not be masked.
- The use of corneal photography allowed for a masked comparison of the primary outcome.
- Contamination of randomization units is possible in this design, but the extent of contamination will be measured with several process indicators.

Introduction

Prevention may be the best option for reducing the burden of corneal blindness caused by corneal ulcers. Corneal opacity is the fourth-leading cause of blindness worldwide, with a disproportionate burden borne by low- and middle-income countries.[1-3] In such settings, corneal abrasions that occur as a result of agricultural trauma often go untreated, increasing the chances of a bacterial or fungal corneal ulcer and subsequent opacity.[4-8] Even successful antimicrobial treatment often leaves a patient with visual impairment because of the associated immune response and resultant corneal scar.[9-11] Delays in presentation and initiation of antimicrobial therapy result in worse clinical outcomes, including severe visual impairment and corneal perforation.[12-15] Indeed, the ultimate visual outcome depends less on the specific antimicrobial or anti-inflammatory agent used, and far more on the visual acuity at the time antimicrobial therapy is started.[9, 16] Reducing the delay in starting antimicrobial therapy following a corneal abrasion could prevent infections from developing, and thus could be the best way to reduce corneal opacity-related vision loss in resource-poor settings.

A promising approach for corneal ulcer prevention is the use of community health workers to diagnose corneal abrasions and provide prompt administration of antimicrobials. Community-level interventions have the potential to increase service uptake in settings with poor access to the health care system and may reduce delays in seeking treatment.[17] Community-based approaches are feasible for eye diseases, with notable successes demonstrated by mass drug administrations for onchocerciasis and trachoma.[18-22] Several studies have implemented a community health worker program for prophylaxis of corneal abrasions, and found very low rates of infectious keratitis.[23-26] These studies could not assess the effectiveness of the implemented community health worker program, since all participants received the program. A cluster-randomized trial would provide the strongest form of evidence for the effectiveness of a community health worker program for corneal ulcer prevention.

Designing a randomized trial to determine the effectiveness of a corneal ulcer prevention program is challenging. Corneal ulceration is a relatively rare outcome, with estimates ranging from 11 cases per 100,000 person-years in Minnesota to 799 cases per 100,000 person-years in Nepal.[23, 24, 27-30] A very large sample size would be needed to enroll enough cases to detect an effect. Furthermore, corneal ulcer detection is difficult. Previous studies have relied on program referrals, but in a trial setting with a control group, this approach would bias the study.[23-26] Clinic-based case finding would likely underestimate the true number of corneal ulcers in settings with poor access to health care. This approach could also result in bias between the groups, with a paradoxically higher number of patients in the intervention group due to increased attention and referrals. In addition, a successful program would require publicity and education, which might be difficult to administer in a randomized fashion to a public at risk for a disease but not yet afflicted.

In the present report, we describe the methods of a cluster-randomized trial that uses a large simple trial design to overcome these challenges.[31] The Village-Integrated Eye Worker (VIEW) trial is a cluster-randomized trial designed to determine the effectiveness of a community health worker-based intervention to prevent corneal ulcers. Community randomization protects against the risk of contamination posed by an individual-randomized trial, increases feasibility of intervention delivery, and is well suited for the nature of a corneal ulcer prevention intervention. A simple outcome (incidence of corneal ulceration), assessed identically within the actual intervention and control communities using electronic data capture and smartphone-based photography, allows a large sample size and sufficient statistical power to detect a modest treatment effect for a rare outcome.

Methods and analysis

Study Overview

In the VIEW trial, Village Development Committees (VDCs) in rural and semi-urban Nepal are randomized in a 1:1 ratio to intervention or control. In communities randomized to the intervention, existing Female Community Health Volunteers (FCHVs) are trained to diagnose corneal abrasions and provide antimicrobial ointments as prophylaxis. An active publicity campaign in intervention communities encourages residents to present to the community health worker within 24 hours of ocular trauma. In control communities, the existing FCHV receives no additional training and no publicity campaign is conducted. No changes to existing eye health care services are otherwise made, and residents from both arms are free to seek care at any local health care facilities for eye complaints. Masked outcome assessors perform an annual census in both intervention and control communities over a 3-year period. Census workers photograph both corneas of all residents upon enrollment into the study and at the fourth annual census, and at any intervening census in which a resident reports symptoms consistent with a corneal ulcer. Corneal photographs are later graded for corneal opacity by masked examiners. An overview of study procedures and study timeline is provided in Table 1.

Specific Aims and Outcomes

The specific aims of this trial are (1) to determine whether diagnosis and prophylaxis of corneal abrasions by community health workers will reduce the incidence of corneal ulceration in rural Nepal, (2) to assess the cost-effectiveness of the corneal ulcer prevention program, and (3) to estimate the true incidence of corneal ulceration in this population. We hypothesize that communities in which community health workers are available to provide diagnosis and prophylaxis for corneal abrasions will have a significantly lower incidence of corneal ulceration compared to communities without this service. The primary outcome (Specific Aim 1) is incident corneal opacity in an individual, as determined from corneal photography. “Incident corneal opacity” is defined as the absence of photographic evidence of a corneal opacity at one census visit followed by the presence of photographic evidence of an opacity at a subsequent visit. Secondary outcomes include (1) the prevalence of visual impairment caused by corneal ulceration as assessed through clinical exams of residents with incident corneal opacities, (2) time from ocular trauma until presentation to the FCHV, and (3) awareness of the intervention among the study population as assessed through an annual survey.

Setting and Eligibility

We are conducting this study in all communities from 24 Village Development Committees (VDCs; government-defined administrative units) in the Chitwan and Nawalparasi districts of Nepal. VDCs are eligible for the study if they lie within the catchment area of the Bharatpur Eye Hospital and have a population of less than 15,000 per the 2001 government census. Of 112 VDCs in these districts, 24 meet the eligibility criteria and are included in the trial. All residents in study communities are offered enrollment in each annual census. A census worker visits each household in each village included in the study. At the baseline visit, verbal consent from each head of household is obtained for participation of all household members in the census visits.

Randomization and Masking

After the baseline census, VDCs are randomized with stratification by district (Chitwan vs. Nawalparasi) to receive the intervention or no intervention. Stratification is performed to

minimize the chances of bias that could have occurred if the randomization had been unbalanced between the two geographically distant sets of communities. The study biostatistician generates the random allocation sequence using R (R Foundation for Statistical Computing, Vienna, Austria). Allocation is concealed by enrolling all communities before randomization and offering the intervention to all community members. Study staff from the Bharatpur Eye Hospital are responsible for implementation of the randomization sequence.

Due to the nature of the intervention, FCHVs in intervention VDCs are not masked to treatment allocation. The District Chief Public Health Officers, who oversee FCHVs in both intervention and control VDCs, are informed of the study arms. Personnel who perform census activities are unaware of treatment allocation. In addition, all study personnel conducting photograph grading are masked to treatment allocation. These photograph graders are crucial to mask since they are assessing the primary outcome of the trial. The photograph graders are also the easiest to mask, since photographs can be displayed in a random order without identifying information.

Intervention

Female Community Health Volunteers

The FCHV program was initiated by the government of Nepal in 1988.[32] The program aims to link communities to health care and to provide community-based services and health promotion.[33] FCHVs are selected by their communities, live in the wards they serve, and have experience implementing community health projects, including family planning and immunization campaigns.[33, 34] Existing FCHVs in intervention VDCs are trained as part of the corneal ulcer prevention program.

Training and Supervision

FCHVs located in VDCs randomized to the intervention attend a 3-day training course at Bharatpur Eye Hospital. The initial training includes both lecture and hands-on practice. Lecture includes basic eye anatomy, common eye diseases, and the difference between ocular trauma, corneal abrasion, and corneal ulcer. FCHVs are trained to diagnose corneal abrasions using fluorescein strips, 2.5x magnifying loupes, and light-emitting diode (LED) ultraviolet (UV) flashlight. FCHVs are also trained to measure Counting Fingers visual acuity, to administer eye ointments, and to enter data into study logbook forms.

Training is conducted in Nepali by trained study staff from the Bharatpur Eye Hospital and is supervised by the investigators. A quiz is administered at the end of the initial 3-day training. FCHVs with scores of 80% or greater are invited to begin intervention work immediately whereas those with scores of less than 80% complete additional one-on-one training with the study staff. Illiterate FCHVs are asked to bring a family member or neighbor to the trainings to provide reading and writing support for the data entry portion of the program.

The study team visits each FCHV weekly to review corneal abrasion cases, collect logbook data, and replenish supplies. The study team conducts refresher trainings to review the basic concepts and skills required in diagnosing corneal abrasions. Brief refresher trainings are conducted monthly and more in-depth trainings are conducted every 6 months.

Corneal ulcer prevention program

If a participant presents with ocular trauma, redness, and/or pain and is interested in participating in the study, written consent is obtained before procedures are performed. If a participant is illiterate, thumbprints are obtained in the presence of a witness. Minors (participants <18 years of age) and a parent or legal guardian both provide written consent. If

the resident does not provide consent, the FCHV may still provide diagnosis and prophylaxis or referral, but she will not record any data onto the logbook form.

Any person presenting to the FCHV with ocular trauma, redness, and/or pain has a corneal examination with fluorescein strips, 2.5x magnifying loupes, and an LED UV flashlight. Participants are immediately referred to Bharatpur Eye Hospital or the nearest primary eye care center if they are diagnosed with a corneal ulcer, bilateral corneal abrasions, visual acuity worse than Counting Fingers in the unaffected eye, or some other ocular abnormality that the FCHV cannot diagnose. Participants with a corneal abrasion receive 9 single-dose applicaps of 1% chloramphenicol ointment (Chloromycetin Kaps, Pfizer India) and 1% itraconazole ointment (Itral, Jawa Pharmaceuticals) to be used 3 times daily for 3 days. Pregnant women are given 1% azithromycin ointment (Zaha, Ajanta Pharma Ltd) instead of chloramphenicol. The FCHV applies the first dose to demonstrate the technique, and the remaining 8 doses are performed by the participant without direct observation. A logbook form is completed for each patient, including the patient's demographic information and telephone number, questions about risk factors for ocular trauma, date and time of presentation and of ocular trauma, visual acuity, and follow-up visit status. After 3 days, the participant is requested to return to the FCHV for a follow-up examination. At the follow-up visit, participants report the number of doses of medication they used and answer an open-ended question about adverse events. Participants are asked to bring their used applicap containers and ointment tubes to the follow-up visit in order to corroborate reported adherence. The eye is re-examined with fluorescein using the same technique as before. If an allergic reaction, corneal abrasion, or corneal ulcer is found on examination, then the participant is referred to Bharatpur Eye Hospital or the nearest primary eye care center.

Publicity

Study staff at Bharatpur Eye Hospital hold orientation meetings with teachers, traditional healers, and local political leaders to introduce the program and to encourage community leaders to advertise the programs. FCHVs in study communities advertise their services for ocular trauma through door-to-door visits with households in their wards and monthly meetings with their ward-level Mother's Groups. The FCHV describes her role as a community health worker and encourages the community to present to her within 24 hours of experiencing ocular trauma. FCHVs also post advertisements describing ulcer prevention throughout the community and distribute pamphlets, greeting cards, and calendars describing the program. All public publicity materials such as posters are removed prior to the annual census to maintain masking of the census workers.

Outcome Assessments

Census and photography

Demographics and screening questions. An annual census is conducted in all study communities over the 3-year study period. The baseline census is conducted before randomization. Census workers visit each household in each study community. After obtaining verbal consent from the head of household, the census worker records the full name, age, and gender of each household member. The census worker also asks each household member several ocular history questions to determine which household members might have had a corneal ulcer. During interim census periods, the ocular history screening questions refer to experience of ocular symptoms within the past year; the first time the questions are asked, they refer to lifetime experience. The questions include experience of ocular trauma, sudden decreased vision, eye pain, and corneal infection. Data are recorded using a custom-designed mobile application on Google Nexus 5 smartphones. Census workers use the mobile device to

record the global positioning system (GPS) coordinates of every household to increase efficiency of follow-up activities and allow assessment of spatial relationships.

Corneal photographs. At the baseline and final census phases, the census workers photograph the corneas of all residents in the study area. During the interim census phases, the census workers photograph the corneas of those who answer one or more of the ocular screening questions positively. A smartphone attachment, the Ocular CellScope (Development Impact Lab, Berkeley, CA USA), is used to improve the quality of corneal photographs.[35] The CellScope is a 3D-printed device with a +25 diopter lens and external illumination, which allows the smartphone camera to capture high-quality corneal photographs.

Training. Census workers attend a 3-day training at Bharatpur Eye Hospital prior to the start of each annual census. Training includes lectures, hands-on practice with the mobile application and photography, and field practice in a non-study community. The study team monitors each census worker weekly to confirm quality and completeness of data collection and photography. Data collection progress is monitored locally by study staff at Bharatpur Eye Hospital and by investigators at the University of California, San Francisco (UCSF) on Salesforce.com.

Photograph grading

Definitions. Photographs from individuals answering affirmatively to any of the screening questions at a follow-up census are presented for grading in a random order. The grading program presents all photos for a single eye at a time. Graders are masked to the grades and images of the contralateral eye, to study identifier, and to other graders' grades. After indicating whether all photographs were taken of the same eye, the photographs are graded for quality (good, poor but readable, or unreadable), and then for the presence of an opacity (definitely yes, probably, possibly, definitely no). For any photograph graded as a possible, probable, or definite opacity, the photographs from all preceding phases are presented for comparison. These previous photos are graded according to the same criteria. A random sample of photos stratified by the initial opacity grade is presented a second time to determine intra-rater reliability.

Ophthalmologist adjudication. Photographs proceed through several rounds of grading. The process starts with two graders in Nepal independently grading all eligible corneal photographs. Photographs graded as possible, probable, or definite opacity by either grader are then presented to one of three cornea specialists for a first round of adjudication. In addition, a random sample of photographs graded as definitely having no opacity or as unreadable quality are sent for the initial adjudication. Any photograph judged to be a possible, probable, or definite opacity at this first level of adjudication, as well as any photographs graded as definitely no for opacity by the first adjudicator but probable or definite opacity by both of the initial graders, is subsequently sent to all three ophthalmologists for a second level of adjudication. If two of the three ophthalmologists grade an eye as having a probable or definite opacity at one phase, and definitely no opacity or a possible opacity at a previous phase, the eye will be classified as having an incident opacity for the primary outcome.

Training. Photograph graders and adjudicators receive extensive training. The training includes an overview of the anatomy of the cornea and the pathophysiology of corneal infections. During the training, each photograph grader is presented with 100 photographs, half of which are of corneal ulcers or corneal scars, and half of which are of normal corneas. These training photographs were taken with the cameras used for the study. The results of this exercise are compared against an expert consensus reference grade which was determined using the

consensus grade from three ophthalmologists. Discrepancies are reviewed in person with the photograph graders. Graders who achieve a Cohen's kappa greater than 0.7 for inter-rater reliability (comparing the 100 grades against the expert grader) are certified as graders. Graders are re-trained and re-certified each year, using a different set of corneal photographs.

12-month nested case-control study

Design. A nested case-control study is conducted among incident cases of corneal ulcer and an equal number of age- (±2 years), sex-, and community-matched controls, with the visit scheduled to take place 12 months after the case's symptoms started. Visits are preferably conducted at Bharatpur Eye Hospital, Kawasoti Eye Care Center, or Parsa Eye Care Center; if participants cannot attend one of these facilities then a mobile team will visit the participant at their home. An eye examination is performed for each eye by an optometrist or ophthalmic assistant, and risk factors for corneal ulceration and quality of life are assessed with standardized questionnaires. Study personnel conducting the 12-month visit are masked to case/control status of the participant as well as randomization arm during the procedures.

Eye examination. Trained study personnel perform manifest refraction and best spectacle-corrected visual acuity assessments, followed by an eye examination and corneal photography. The eye examination is performed with a slit lamp biomicroscope in the eye clinics, and with a penlight at the mobile examinations. Based on the eye examination, the examiner states the condition accounting for visual acuity worse than 20/20 (e.g., corneal opacity, cataract, glaucoma, etc.). In addition, the examiner compares the vision in the worse-seeing eye to the better-seeing eye, and determines the ocular condition responsible for the decrement in the worse-seeing eye (e.g., corneal opacity, cataract, glaucoma, etc.).

Instruments. The Euroqol 5D-5L quality of life questionnaire and Hong Kong visual functioning questionnaires were translated from English to Nepali and back-translated independently by two bilingual study staff members at the Bharatpur Eye Hospital. A committee reviewed the questionnaires to determine the appropriateness of the questions for this population and pilot-tested the refined questionnaires on a sample of patients at the Bharatpur Eye Hospital. Questionnaires on risk factors for corneal ulcers include questions on agricultural trauma, contact lens wear, and use of topical corticosteroids, as well as health care seeking behaviors after eye trauma. The costing questionnaire elicits all patient- and hospital-related costs of the corneal opacity, including laboratory testing, medications, and surgeries, as well as the opportunity costs of attending hospital visits.

Clinic-based case finding

Clinic-based case finding is conducted at several sites throughout the study area that were identified as locations that receive corneal abrasion and corneal ulcer cases. Each month, study staff visit each of these sites and use the site's logbook to record data on any corneal abrasion, corneal ulcer, or corneal foreign body case that presented to that site in the past month. These data will be used in Specific Aim 3 to inform the calculation of incidence in the non-intervention arm.

Intervention awareness surveys

An intervention awareness survey is conducted annually in all VDCs, with survey workers not informed about the trial intervention, and masked to whether the community has been randomized to intervention or control. A random sample of households from the most recent census is selected to participate in the survey. Census data, including name, phone number, and household GPS coordinates, are uploaded to the mobile software platform GIS Cloud (GIS Cloud Ltd., London, United Kingdom, http://www.giscloud.com) for the survey. The trained

survey workers use handheld mobile devices to identify households from a map generated by the software, and ask an adult in the household a series of questions designed to determine their level of awareness of the intervention. Conducting the survey in control VDCs allows us to assess contamination as well as provide a comparison for the effect of the publicity campaign. Survey workers are required to complete the survey on at least 10 of the 15 selected households in each ward.

An unmasked intervention awareness survey is conducted by trained study personnel annually in intervention VDCs only. Unlike the masked survey, survey workers understand the nature of the intervention and publicity campaign, and provide additional information about the program if the resident is unaware of the intervention. The unmasked survey is conducted identically to the masked survey in terms of selection of households and data collection and management, but provides information about the impact of the intervention sooner, so that corrective actions can be taken.

Programmatic costs

All programmatic costs, including staff salaries, equipment, antimicrobial ointments, outreach and advertising, and training costs are recorded by the study coordinator during the trial. Costs are collected by the study coordinator for each year of the program.

Data Collection, Management, Monitoring

All electronic data and photographs are uploaded daily to secure, cloud-based servers. Data collected on paper are double-data entered and adjudicated in REDCap.[36] Study personnel collecting data receive at least a one-day initial training, and periodic refresher trainings. Study staff at Bharatpur Eye Hospital conduct weekly monitoring visits to all FCHVs, census workers, and survey workers collecting data, and data collection progress is reviewed by the data manager at UCSF weekly.

Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) for this trial includes independent experts in bioethics, biostatistics, epidemiology, ophthalmology, and international public health appointed by the NIH-NEI and empaneled before the start of the study. The DSMC meets at least once each year, and organizes teleconferences as needed for progress reporting. The study protocol and modifications are subject to review and approval by Institutional Review Boards at UCSF and in Nepal, and by the DSMC. The DSMC monitors severe or unexpected events that threaten the safety of patients and oversees the data collected throughout the duration of the study. The DSMC is responsible for reviewing the results of the interim analysis and determining whether or not the trial should continue, with or without modifications.

Statistical Analysis Plan

Sample Size

Sample size and power calculations are based on an estimated incidence of corneal ulceration of 100 per 100,000 person-years. We estimate that 12 VDCs per arm will provide greater than 80% power to detect a 30% reduction in incidence of corneal ulceration, assuming 9000 people per VDC, an intra-class correlation coefficient of 0.00015 and a two-tailed alpha of 0.05.

Interim Analysis and Stopping Guidelines

An interim analysis for efficacy is performed one-third of the way through the trial, with alpha set at 0.001. The interim analysis has approximately 70% power to detect a 68% reduction in corneal ulcer rates over the single year. The DSMC reviews the unmasked interim analysis and makes recommendations on the continuation of the trial. No interim analysis for futility is performed.

Specific Aim 1

The primary analysis is negative binomial regression to compare the incidence of corneal ulcers between treatment arms, with the count of incident corneal ulcers over the study period as the outcome, log person-time at risk as an offset, and treatment arm as the sole covariate. An individual is determined to have an ulcer if a new opacity is identified by photograph grading at a follow-up census. For individual-level data, an opacity identified at a follow-up census will be considered new if it is absent on a photograph of acceptable quality from at least one previous census. For community-level data, we will compute the total count of new opacities identified in each randomization unit at each of the follow-up census phase. Individuals can contribute multiple incident ulcers to the overall count, but no more than one new opacity per eye per phase. Individuals start contributing person-time at the first census they are photographed and continue contributing person-time until the final census with complete data (i.e. screening questions answered, and if required, then photographs taken and uploaded). Individuals who develop ulcers will continue to contribute person time and can contribute additional ulcers until they leave the study (i.e., permanently moved, died, or study conclusion).

Negative binomial regression explicitly addresses the cluster-randomized nature of the design, and the proposed analysis follows the intent-to-treat principle. We will use a permutation *P*-value, taking into account the stratified design of the randomization.

Specific Aim 2

The primary analysis is a trial-based cost-effectiveness analysis of the costs per corneal ulcer prevented, assessed at the VDC level. Costs include all programmatic and treatment costs per VDC over the duration of the 3-year study. The effectiveness outcome will be the same as for Specific Aim 1: the number of incident corneal opacities per VDC. Both costs and effects will be discounted at 5% per year for the 3-year time horizon of the analysis. We will use the nonparametric bootstrap to estimate the joint sampling distribution of the differences in average VDC costs and effects between the treatment arms, and plot this on the cost-effectiveness plane and in a cost-effectiveness acceptability curve. In a secondary analysis we convert visual acuity data from the 12-month visit into quality adjusted life-years (QALYs), and perform the same analyses in terms of costs per QALYs lost. We will also conduct a hypothetical cohort-based cost-effectiveness analysis as a supplement to assist in interpretive generalization beyond the specific programmatic cost structure of the Nepal trial setting.

Specific Aim 3

The primary analysis is an assessment of the true incidence of corneal ulceration in the control arm. The primary outcome of the trial (Specific Aim 1) will produce an estimate of the incidence of corneal ulceration sufficient to answer the overall research question, but the estimate itself may be biased by outcome misclassification and missing data. The use of census photographs alone as the outcome will result in some number of false negatives and false positives. Despite rigorous efforts to ensure high coverage during census phases, it is not possible to capture every single person, thus it is possible to miss incident ulcers using only census photographs as the outcome. In addition, the grading process inevitably results in some photos falsely classified as having an opacity. To address false negatives, we will incorporate ulcers identified on clinic-based case finding that were not captured on census photographs into the outcome. To address

false positives, we will update outcome data with information from the clinical exam conducted during the 12-month nested case control study to remove those falsely classified as positive on photograph.

We will report community-, age-, and gender-stratified incidence rates. The spatial distribution of incident corneal ulcers will be examined using coordinates obtained at the time of the census. The association between incident corneal ulceration and individual-level risk factors collected at the time of the census, including age, sex, and urban/rural residence, will be assessed with clustered logistic regression.

Ethics and dissemination

The UCSF Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council have given ethical approval for the trial. The District Public Health Offices of the Nawalparasi and Chitwan districts provide approval for the study each year before census data collection commences. The trial is registered at clinicaltrials.gov (NCT01969786).

Verbal consent is obtained for census and photography, awareness surveys, and the 12-month follow-up visit. Written consent is obtained for FCHV-administered medications. Data and photos collected on individuals are linked to individual participant information using unique identifiers. Only key study personnel have access to identifying information.

The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Author's contributions. KSO, TCP, JPW, MS, MU, TML, and JDK developed the study design, drafted the protocol, and contributed to study implementation and monitoring. BR, RPK, BP, MG, and JAG contributed to study implementation and monitoring.

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Competing interests statement. The authors have no conflicts of interests to disclose.

Ethical approval. The study received Institutional Review Board approval from the University of California, San Francisco Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council.

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Table 1. Timeline of major study procedures[1]

Time point	Activity	Description of activities
Month 0	Phase 0 census (baseline)	In all 24 study VDCs, collect the following data: • Demographics • Ocular history screening (lifetime) • Bilateral photography of all participants
Month 6	Randomization	Randomize 12 VDCs to receive intervention and 12 VDCs to receive no intervention
	Intervention implementation	In 12 intervention VDCs, train FCHVs to: • Diagnose corneal abrasions • Provide antimicrobial ointments for abrasions • Refer when needed
Month 8	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 12	Phase 12 census	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening (past 12 months) • Symptom-based photography
Month 20	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 24	Phase 24 census	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening past 12 months) • Symptom-based photography
Month 32	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 36	Phase 36 census (final)	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening (past 12 months) • Bilateral photography of all participants

[1]Census photograph grading and the 12-month visit began after the Month 12 census and continued on an ongoing basis

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The Village-Integrated Eye Worker trial (VIEW): rationale and design of a cluster-randomized trial to prevent corneal ulcers in resource-limited settings

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The Village-Integrated Eye Worker trial (VIEW): rationale and design of a cluster-randomized trial to prevent corneal ulcers in resource-limited settings

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Abstract

Introduction. Corneal opacity is a leading cause of blindness worldwide. In resource-limited settings, untreated traumatic corneal abrasions may result in infection and ultimately, opacity.. Though antimicrobial treatment of corneal ulcers may successfully cure infections, the scarring that accompanies the resolution of infection can still result in visual impairment. Prevention may be the optimal approach for reducing corneal blindness. Studies have employed community health workers to provide prompt administration of antimicrobials after corneal abrasions to prevent infections, but these studies were not designed to determine the effectiveness of such a program.

Methods and analysis. The Village-Integrated Eye Worker trial (VIEW) is a cluster-randomized trial designed to assess the effectiveness of a community health worker intervention to prevent corneal ulcers. Twenty-four Village Development Committees (VDCs) in Nepal were randomized to receive a corneal ulcer prevention program or to no intervention. Female Community Health Volunteers (FCHVs) in intervention VDCs are trained to diagnose corneal abrasions, provide antimicrobials, and to refer participants when needed. An annual census is conducted over 3 years in all study VDCs to assess the incidence of corneal ulceration via corneal photography (primary outcome). Masked outcome assessors grade corneal photographs to determine the presence or absence of incident corneal opacities. The primary analysis is negative binomial regression to compare the incidence of corneal ulceration by study arm.

Ethics and dissemination. The University of California San Francisco Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council have given ethical approval for the trial. The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Registration. This trial was registered at clinicaltrials.gov (NCT01969786) on October 21, 2013.

Strengths and limitations of this study

- VIEW is the first randomized controlled trial designed to determine the effectiveness of a community health worker intervention to prevent corneal ulcers.
- The large simple trial design allows detection of a modest intervention effect for a rare outcome.
- Given the nature of the intervention, the study participants and field staff could not be masked.
- The use of corneal photography allowed for a masked comparison of the primary outcome.
- Cluster-randomization reduces the risk of contamination, though contamination of randomization units is still possible in this design. The extent of contamination will be measured with process indicators.

Introduction

Prevention may be the best option for reducing the burden of corneal blindness caused by corneal ulcers. Corneal opacity is the fourth-leading cause of blindness worldwide, with a disproportionate burden borne by low- and middle-income countries.[1-3] In such settings, corneal abrasions that occur as a result of agricultural trauma often go untreated, increasing the chances of a bacterial or fungal corneal ulcer and subsequent opacity.[4-8] Even successful antimicrobial treatment often leaves a patient with visual impairment because of the associated immune response and resultant corneal scar.[9-11] Delays in presentation and initiation of antimicrobial therapy result in worse clinical outcomes, including severe visual impairment and corneal perforation.[12-15] Indeed, the ultimate visual outcome depends less on the specific antimicrobial or anti-inflammatory agent used, and far more on the visual acuity at the time antimicrobial therapy is started.[9, 16] Reducing the delay in starting antimicrobial therapy following a corneal abrasion could prevent infections from developing, and thus could be the best way to reduce corneal opacity-related vision loss in resource-poor settings.

A promising approach for corneal ulcer prevention is the use of community health workers to diagnose corneal abrasions and provide prompt administration of antimicrobials. Community-level interventions have the potential to increase service uptake in settings with poor access to the health care system and may reduce delays in seeking treatment.[17] Community-based approaches are feasible for eye diseases, with notable successes demonstrated by mass drug administrations for onchocerciasis and trachoma.[18-22] Several studies have found low rates of infectious keratitis after implementing community health worker programs for prophylaxis of corneal abrasions.[23-26] However, these studies were unable to assess the causal impact of the programs, since all participants were included in the interventions. A cluster-randomized trial would provide the strongest form of evidence for the effectiveness of a community health worker program for corneal ulcer prevention.

Designing a randomized trial to determine the effectiveness of a corneal ulcer prevention program is challenging. Corneal ulceration is a relatively rare outcome, with estimates ranging from 11 cases per 100,000 person-years in Minnesota to 799 cases per 100,000 person-years in Nepal.[23, 24, 27-30] A very large sample size would be needed to enroll enough cases to detect an effect. Furthermore, corneal ulcer detection is difficult. Previous studies have relied on program referrals, but in a trial setting with a control group, this approach is prone to bias.[23-26] Clinic-based case finding would likely underestimate the true number of corneal ulcers in settings with poor access to health care. This approach could also result in bias between the groups, with a paradoxically higher number of patients in the intervention group due to increased attention and referrals. In addition, a successful program would require publicity and education, which might be difficult to administer in a randomized fashion to a public at risk for a disease but not yet afflicted and may result in contamination.

In the present report, we describe the methods of a cluster-randomized trial that uses a large simple trial design to overcome these challenges.[31] The Village-Integrated Eye Worker (VIEW) trial is a cluster-randomized trial designed to determine the effectiveness of a community health worker-based intervention to prevent corneal ulcers. Community randomization protects against the risk of contamination posed by an individual-randomized trial, increases feasibility of intervention delivery, and is well suited for the nature of a corneal ulcer prevention intervention. A simple outcome (incidence of corneal ulceration), assessed identically within the actual intervention and control communities using electronic data capture and smartphone-based photography, allows a large sample size and sufficient statistical power to detect a modest treatment effect for a rare outcome.

Methods and analysis

Study Overview

In the VIEW trial, Village Development Committees (VDCs) in rural and semi-urban Nepal were randomized in a 1:1 ratio to intervention or control. In communities randomized to the intervention, existing Female Community Health Volunteers (FCHVs) are trained to diagnose corneal abrasions and provide antimicrobial ointments as prophylaxis. An active publicity campaign in intervention communities encourages residents to present to the community health worker within 24 hours of ocular trauma. In control communities, existing FCHVs receive no additional training and no publicity campaign is conducted. No changes to existing eye health care services are otherwise made, and residents from both arms are free to seek care at any local health care facilities for eye complaints. Masked outcome assessors perform an annual census in both intervention and control communities over a 3-year period. Census workers photograph both corneas of all residents upon enrollment into the study and at the fourth annual census, and at any intervening census in which a resident reports symptoms consistent with a corneal ulcer. Corneal photographs are later graded for corneal opacity by masked examiners. An overview of study procedures and study timeline is provided in Table 1.

Specific Aims and Outcomes

The specific aims of this trial are (1) to determine whether diagnosis and prophylaxis of corneal abrasions by community health workers will reduce the incidence of corneal ulceration in rural Nepal, (2) to assess the cost-effectiveness of the corneal ulcer prevention program, and (3) to estimate the true incidence of corneal ulceration in this population. We hypothesize that communities in which community health workers are available to provide diagnosis and prophylaxis for corneal abrasions will have a significantly lower incidence of corneal ulceration compared to communities without this service. The primary outcome (Specific Aim 1) is incident corneal opacity in an individual during the 3-year study period, as determined from corneal photography. “Incident corneal opacity” is defined as the absence of photographic evidence of a corneal opacity at one census visit followed by the presence of photographic evidence of an opacity at a subsequent visit. Secondary outcomes include (1) the prevalence of visual impairment caused by corneal ulceration as assessed through clinical exams of residents with incident corneal opacities, (2) time from ocular trauma until presentation to the FCHV, and (3) awareness of the intervention among the study population as assessed through an annual survey.

Setting and Eligibility

We are conducting this study in all communities from 24 Village Development Committees (VDCs; government-defined administrative units) in the Chitwan and Nawalparasi districts of Nepal. VDC-level eligibility criteria include location within the catchment area of the Bharatpur Eye Hospital and population of less than 15,000 per the 2001 government census. Of 112 VDCs in these districts, 24 meet these eligibility criteria and are included in the trial. Geographic separation was not considered in selection of eligible VDCs. All residents in study communities are offered enrollment in each annual census. A census worker visits each household in each village included in the study. At the baseline visit, verbal consent from each head of household was obtained for participation of all household members in the census visits. Data collection for the baseline visit began in January 2014.

Randomization and Masking

After the baseline census, VDCs were randomized with stratification by district (Chitwan vs. Nawalparasi) to receive the intervention or no intervention. Stratification is performed to minimize the chances of bias that could have occurred if the randomization had been unbalanced between the two geographically distant sets of communities. The study biostatistician generated the random allocation sequence using R (R Foundation for Statistical Computing, Vienna, Austria). Allocation is concealed by enrolling all communities before randomization and offering the intervention to all community members. Study staff from the Bharatpur Eye Hospital are responsible for implementation of the randomization sequence.

Due to the nature of the intervention, FCHVs in intervention VDCs are not masked to treatment allocation. The District Chief Public Health Officers, who oversee FCHVs in both intervention and control VDCs, are informed of the study arms. Personnel who perform census activities are unaware of treatment allocation. In addition, all study personnel conducting photograph grading are masked to treatment allocation. These photograph graders are crucial to mask since they are assessing the primary outcome of the trial. The photograph graders are also the easiest to mask, since photographs can be displayed in a random order without identifying information.

Intervention

Female Community Health Volunteers

The FCHV program was initiated by the government of Nepal in 1988.[32] The program aims to link communities to health care and to provide community-based services and health promotion.[33] FCHVs are selected by their communities, live in the wards they serve, and have experience implementing community health projects, including family planning and immunization campaigns.[33, 34] Existing FCHVs in intervention VDCs are trained as part of the corneal ulcer prevention program.

Training and Supervision

FCHVs located in VDCs randomized to the intervention attend a 3-day training course at Bharatpur Eye Hospital. The initial training includes both lecture and hands-on practice. Lecture includes basic eye anatomy, common eye diseases, and the difference between ocular trauma, corneal abrasion, and corneal ulcer. FCHVs are trained to diagnose corneal abrasions using fluorescein strips, 2.5x magnifying loupes, and light-emitting diode (LED) ultraviolet (UV) flashlight. FCHVs are also trained to measure Counting Fingers visual acuity, to administer eye ointments, and to enter data into study logbook forms.

Training is conducted in Nepali by trained study staff from the Bharatpur Eye Hospital and is supervised by the investigators. A quiz is administered at the end of the initial 3-day training. FCHVs with scores of 80% or greater are invited to begin intervention work immediately whereas those with scores of less than 80% complete additional one-on-one training with the study staff. Illiterate FCHVs are asked to bring a family member or neighbor to the trainings to provide reading and writing support for the data entry portion of the program.

The study team visits each FCHV weekly to review corneal abrasion cases, collect logbook data, and replenish supplies. The study team conducts refresher trainings to review the basic concepts and skills required in diagnosing corneal abrasions. Brief refresher trainings are conducted monthly and more in-depth trainings are conducted every 6 months.

Corneal ulcer prevention program

If a participant presents with ocular trauma, redness, and/or pain and is interested in participating in the study, written consent is obtained before procedures are performed. If a participant is illiterate, thumbprints are obtained in the presence of a witness. Minors (participants <18 years of age) and a parent or legal guardian both provide written consent. If the resident does not provide consent, the FCHV may still provide diagnosis and prophylaxis or referral, but she will not record any data onto the logbook form.

Any person presenting to the FCHV with ocular trauma, redness, and/or pain is offered a corneal examination, which involves the application of fluorescein to the affected eye(s) and examination with 2.5x magnifying loupes and an LED UV flashlight to identify the presence of a corneal abrasion. Participants are immediately referred to Bharatpur Eye Hospital or the nearest primary eye care center if they are diagnosed with a corneal ulcer, bilateral corneal abrasions, visual acuity worse than Counting Fingers in the unaffected eye, or some other ocular abnormality that the FCHV cannot diagnose. Participants with a corneal abrasion receive 9 single-dose applicaps of 1% chloramphenicol ointment (Chloromycetin Kaps, Pfizer India) and 1% itraconazole ointment (Itral, Jawa Pharmaceuticals) to be applied 3 times daily for 3 days. Pregnant women are given 1% azithromycin ointment (Zaha, Ajanta Pharma Ltd) instead of chloramphenicol. The FCHV applies the first dose to demonstrate the technique, and the remaining 8 doses are performed by the participant without direct observation. The FCHV enters information about the participant into a, including the participant's demographic information and telephone number, questions about risk factors for ocular trauma, date and time of presentation and of ocular trauma, visual acuity, and follow-up visit status. After 3 days, the participant is requested to return to the FCHV for a follow-up examination. At the follow-up visit, participants report the number of doses of medication they used and answer an open-ended question about adverse events. Participants are asked to bring their used applicap containers and ointment tubes to the follow-up visit in order to corroborate reported adherence. The eye is re-examined with fluorescein using the same technique as before. If an allergic reaction, corneal abrasion, or corneal ulcer is found on the follow-up examination, the participant is referred to Bharatpur Eye Hospital or the nearest primary eye care center.

FCHVs will not refuse diagnosis or prophylaxis to anyone based on their residence, even if participants present from control VDCs. FCHVs will record the VDC of all people who present, which will allow us to assess the level of contamination.

Publicity

Study staff at Bharatpur Eye Hospital hold orientation meetings with teachers, traditional healers, and local political leaders to introduce the program and to encourage community leaders to advertise the programs. FCHVs in study communities advertise their services for ocular trauma through door-to-door visits with households in their wards and monthly meetings with their ward-level Mother's Groups. FCHVs encourage the community to present to them within 24 hours of experiencing ocular trauma. FCHVs also post advertisements describing ulcer prevention throughout the community and distribute pamphlets, greeting cards, and calendars describing the program. All public publicity materials such as posters are removed prior to the annual census to maintain masking of the census workers. Publicity activities will be limited to the confines of the VDC boundaries in order to prevent contamination.

Outcome Assessments

Census and photography

Demographics and screening questions. An annual census is conducted in all study communities over the 3-year study period. The baseline census was conducted before

randomization. Census workers visit each household in each study community. After obtaining verbal consent from the head of household, the census worker records the full name, age, and gender of each household member. The census worker also asks each household member several ocular history questions to determine which household members might have had a corneal ulcer. During interim census periods, the ocular history screening questions refer to experience of ocular symptoms within the past year; the first time the questions are asked, they refer to lifetime experience. The questions include experience of ocular trauma, sudden decreased vision, eye pain, and corneal infection. Data are recorded using a custom-designed mobile application on Google Nexus 5 smartphones. Census workers use the mobile device to record the global positioning system (GPS) coordinates of every household to increase efficiency of follow-up activities and allow assessment of spatial relationships.

Corneal photographs. At the baseline and final census phases, the census workers photograph the corneas of all residents in the study area. During the interim census phases, the census workers photograph the corneas of those who answer one or more of the ocular screening questions positively. A smartphone attachment, the Ocular CellScope (Development Impact Lab, Berkeley, CA USA), is used to improve the quality of corneal photographs.[35] The CellScope is a 3D-printed device with a +25 diopter lens and external illumination, which allows the smartphone camera to capture high-quality corneal photographs.

Training. Census workers attend a 3-day training at Bharatpur Eye Hospital prior to the start of each annual census. Training includes lectures, hands-on practice with the mobile application and photography, and field practice in a non-study community. The study team monitors each census worker weekly to confirm quality and completeness of data collection and photography. Data collection progress is monitored locally by study staff at Bharatpur Eye Hospital and by investigators at the University of California, San Francisco (UCSF) on Salesforce.com.

Photograph grading

Definitions. Photographs from individuals answering affirmatively to any of the screening questions at a follow-up census are presented for grading in a random order. The grading program presents all photos for a single eye at a time. Graders are masked to the grades and images of the contralateral eye, to study identifier, and to other graders' grades. After indicating whether all photographs were taken of the same eye, the photographs are graded for quality (good, poor but readable, or unreadable), and then for the presence of an opacity (definitely yes, probably, possibly, definitely no). For any photograph graded as a possible, probable, or definite opacity, the photographs from all preceding phases are presented for comparison. These previous photos are graded according to the same criteria. A random sample of photos stratified by the initial opacity grade is presented a second time to determine intra-rater reliability.

Ophthalmologist adjudication. Photographs proceed through several rounds of grading. The process starts with two graders in Nepal independently grading all eligible corneal photographs. Photographs graded as possible, probable, or definite opacity by either grader are then presented to one of three cornea specialists for a first round of adjudication. In addition, a random sample of photographs graded as definitely having no opacity or as unreadable quality are sent for the initial adjudication. Any photograph judged to be a possible, probable, or definite opacity at this first level of adjudication, as well as any photographs graded as definitely no for opacity by the first adjudicator but probable or definite opacity by both of the initial graders, is subsequently sent to all three ophthalmologists for a second level of adjudication. If two of the three ophthalmologists grade an eye as having a probable or definite opacity at one phase, and

definitely no opacity or a possible opacity at a previous phase, the eye will be classified as having an incident opacity for the primary outcome.

Training. Photograph graders and adjudicators receive extensive training. The training includes an overview of the anatomy of the cornea and the pathophysiology of corneal infections. During the training, each photograph grader is presented with 100 cornea photographs taken with the Ocular CellScope, half of which are of corneal ulcers or corneal scars, and half of which are of normal corneas. The results of this exercise are compared against an expert consensus reference grade which was determined using the consensus grade from three ophthalmologists. Discrepancies are reviewed in person with the photograph graders. Graders who achieve a Cohen's kappa greater than 0.7 for inter-rater reliability (comparing the 100 grades against the expert grader) are certified as graders. Graders are re-trained and re-certified each year, using a different set of corneal photographs.

12-month nested case-control study

Design. A nested case-control study is conducted among incident cases of corneal ulcer and an equal number of age- (±2 years), sex-, and community-matched controls, with the visit scheduled to take place 12 months after the case's symptoms started. Visits are preferably conducted at Bharatpur Eye Hospital, Kawasoti Eye Care Center, or Parsa Eye Care Center; if participants cannot attend one of these facilities then a mobile team will visit the participant at their home. An eye examination is performed for each eye by an optometrist or ophthalmic assistant, and risk factors for corneal ulceration and quality of life are assessed with standardized questionnaires. Study personnel conducting the 12-month visit are masked to case/control status of the participant as well as randomization arm during the procedures.

Clinical examination. Trained study personnel perform manifest refraction and best spectacle-corrected visual acuity assessments, followed by an eye examination and corneal photography. The eye examination is performed with a slit lamp biomicroscope in the eye clinics, and with a penlight at the mobile examinations. Based on the eye examination, the examiner states the condition accounting for visual acuity worse than 20/20 (e.g., corneal opacity, cataract, glaucoma, etc.). In addition, the examiner compares the vision in the worse-seeing eye to the better-seeing eye, and determines the ocular condition responsible for the decrement in the worse-seeing eye (e.g., corneal opacity, cataract, glaucoma, etc.).

Instruments. The Euroqol 5D-5L quality of life questionnaire and Hong Kong visual functioning questionnaires were translated from English to Nepali and back-translated independently by two bilingual study staff members at the Bharatpur Eye Hospital. A committee reviewed the questionnaires to determine the appropriateness of the questions for this population and pilot-tested the refined questionnaires on a sample of patients at the Bharatpur Eye Hospital. Questionnaires on risk factors for corneal ulcers include questions on agricultural trauma, contact lens wear, and use of topical corticosteroids, as well as health care seeking behaviors after eye trauma. The costing questionnaire elicits all patient- and hospital-related costs of the corneal opacity, including laboratory testing, medications, and surgeries, as well as the opportunity costs of attending hospital visits.

Clinic-based case finding

Clinic-based case finding is conducted at several sites throughout the study area. These sites were identified as locations that receive corneal abrasion and corneal ulcer cases. Each month, study staff visit each of these sites and use the site's patient logbook to record data on any corneal abrasion, corneal ulcer, or corneal foreign body case that presented to that site in the past month.

Intervention awareness surveys

An intervention awareness survey is conducted annually in all VDCs, with survey workers not informed about the trial intervention, and masked to whether the community has been randomized to intervention or control. A random sample of households from the most recent census is selected to participate in the survey. Census data, including name, phone number, and household GPS coordinates, are uploaded to the mobile software platform GIS Cloud (GIS Cloud Ltd., London, United Kingdom, http://www.giscloud.com) for the survey. The trained survey workers use handheld mobile devices to identify households from a map generated by the application, and ask an adult in the household a series of questions designed to determine their level of awareness of the intervention. Survey workers are required to complete the survey on at least 10 of the 15 selected households in each ward.

Conducting the intervention awareness surveys in control VDCs will provide a measure of contamination. Publicity is limited to intervention VDCs to reduce the likelihood of contamination, but it is possible that residents of control VDCs will learn of the intervention through exposure to publicity materials or word of mouth. Any awareness of the intervention found in control VDCs will be indicative of contamination.

An unmasked intervention awareness survey is conducted by trained study personnel annually in intervention VDCs only. Unlike the masked survey, survey workers understand the nature of the intervention and publicity campaign, and provide additional information about the program if the resident is unaware of the intervention. The unmasked survey is conducted identically to the masked survey in terms of selection of households and data collection and management, but provides information about the impact of the intervention sooner, so that corrective actions can be taken.

Programmatic costs

All programmatic costs, including staff salaries, equipment, antimicrobial ointments, outreach and advertising, and training costs are recorded by the study coordinator during the trial. Costs are collected by the study coordinator for each year of the program.

Data Collection, Management, Monitoring

All electronic data and photographs are uploaded daily to secure, cloud-based servers. Data collected on paper are double-data entered and adjudicated in REDCap.[36] Study personnel collecting data receive at least a 1-day initial training, and periodic refresher trainings. Study staff at Bharatpur Eye Hospital conduct weekly monitoring visits to all FCHVs, census workers, and survey workers collecting data, and data collection progress is reviewed by the data manager at UCSF weekly.

Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) for this trial includes independent experts in bioethics, biostatistics, epidemiology, ophthalmology, and international public health appointed by the NIH-NEI and empaneled before the start of the study. The DSMC meets at least once each year, and organizes teleconferences as needed for progress reporting. The study protocol and modifications are subject to review and approval by Institutional Review Boards at UCSF and in Nepal, and by the DSMC. The DSMC monitors severe or unexpected events that threaten the safety of patients and oversees the data collected throughout the

duration of the study. The DSMC is responsible for reviewing the results of the interim analysis and determining whether or not the trial should continue, with or without modifications.

Statistical Analysis Plan

Sample Size

Sample size and power calculations are based on an estimated incidence of corneal ulceration of 100 per 100,000 person-years. We estimate that 12 VDCs per arm will provide greater than 80% power to detect a 30% reduction in incidence of corneal ulceration, assuming 9000 people per VDC, an intra-class correlation coefficient of 0.00015 and a two-tailed alpha of 0.05.

Interim Analysis and Stopping Guidelines

An interim analysis for efficacy is performed one-third of the way through the trial, with alpha set at 0.001. The interim analysis has approximately 70% power to detect a 68% reduction in corneal ulcer rates over the single year. The DSMC reviews the unmasked interim analysis and makes recommendations on the continuation of the trial. No interim analysis for futility is performed.

Specific Aim 1

The primary analysis is negative binomial regression to compare the incidence of corneal ulcers between treatment arms, with the count of incident corneal ulcers over the study period as the outcome, log person-time at risk as an offset, and treatment arm as the sole covariate. An individual is determined to have an ulcer if a new opacity is identified by photograph grading at a follow-up census. For individual-level data, an opacity identified at a follow-up census will be considered new if it is absent on a photograph of acceptable quality from at least one previous census. For community-level data, we will compute the total count of new opacities identified in each randomization unit at each of the follow-up census phase. Individuals can contribute multiple incident ulcers to the overall count, but no more than one new opacity per eye per phase. Individuals start contributing person-time at the first census they are photographed and continue contributing person-time until the final census with complete data (i.e. screening questions answered, and if required, then photographs taken and uploaded). Individuals who develop ulcers will continue to contribute person time and can contribute additional ulcers until they leave the study (i.e., permanently moved, died, or study conclusion).

Negative binomial regression explicitly addresses the cluster-randomized nature of the design, and the proposed analysis follows the intent-to-treat principle. We will use a permutation *P*-value, taking into account the stratified design of the randomization.

Specific Aim 2

The primary analysis is a trial-based cost-effectiveness analysis of the costs per corneal ulcer prevented, assessed at the VDC level. Costs include all programmatic and treatment costs per VDC over the duration of the 3-year study. The effectiveness outcome will be the same as for Specific Aim 1: the number of incident corneal opacities per VDC. Both costs and effects will be discounted at 5% per year for the 3-year time horizon of the analysis. We will use the nonparametric bootstrap to estimate the joint sampling distribution of the differences in average VDC costs and effects between the treatment arms, and plot this on the cost-effectiveness plane and in a cost-effectiveness acceptability curve. In a secondary analysis we convert visual acuity data from the 12-month visit into quality adjusted life-years (QALYs), and perform the same analyses in terms of costs per QALYs lost. We will also conduct a hypothetical cohort-based cost-effectiveness analysis as a supplement to assist in interpretive generalization beyond the specific programmatic cost structure of the Nepal trial setting.

Specific Aim 3

The primary analysis is an assessment of the true incidence of corneal ulceration in the control arm. The primary outcome of the trial (Specific Aim 1) will produce an estimate of the incidence of corneal ulceration sufficient to answer the overall research question, but the estimate itself may be biased by outcome misclassification and missing data. The use of census photographs alone as the outcome will result in some number of false negatives and false positives. Despite rigorous efforts to ensure high coverage during census phases, it is not possible to capture every single person, thus it is possible to miss incident ulcers using only census photographs as the outcome. In addition, the grading process inevitably results in some photos falsely classified as having an opacity. Internal validation data collected during the 12-month nested case control study will be used to correct the estimate of the incidence in the control arm for misclassification.

We will report community-, age-, and gender-stratified incidence rates. The spatial distribution of incident corneal ulcers will be examined using coordinates obtained at the time of the census. The association between incident corneal ulceration and individual-level risk factors collected at the time of the census, including age, sex, and urban/rural residence, will be assessed with clustered logistic regression.

Patient and Public Involvement

Focus groups were conducted among residents of randomly selected communities within the study area to identify local eye health resource utilization patterns and understand the language used to describe ocular trauma. Summaries of focus group discussions are used to inform training programs for census workers, intervention awareness survey workers, and publicity campaigns. Feedback from FCHVs participating in the training program is used to improve refresher trainings.

Ethics and dissemination

The UCSF Committee on Human Research, Nepal Netra Jyoti Sangh, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council have given ethical approval for the trial. The District Public Health Offices of the Nawalparasi and Chitwan districts provide approval for the study each year before census data collection commences. The trial is registered at clinicaltrials.gov (NCT01969786). Protocol modifications are submitted to the relevant parties for review and/or approval. Table 2 summarizes the study protocol and trial registration information.

Verbal consent is obtained for census and photography, awareness surveys, and the 12-month follow-up visit. Written consent is obtained for FCHV-administered medications. Data and photos collected on individuals are linked to individual participant information using unique identifiers. Only key study personnel have access to identifying information.

The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication.

Author's contributions. KSO, TCP, JPW, MS, MU, TML, and JDK developed the study design, drafted the protocol, and contributed to study implementation and monitoring. BR, RPK, BP, MG, and JAG contributed to study implementation and monitoring. The Village-Integrated Eye Worker Trial Group contributed to all aspects of this project, including study design, protocol development, regulatory and ethical approval, and study implementation and.

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Competing interests statement. The authors have no conflicts of interests to disclose.

Ethical approval. The study received Institutional Review Board approval from the University of California, San Francisco Committee on Human Research, Nepal Netra Jyoti Sangh, and the Nepal Health Research Council.

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Table 1. Timeline of major study procedures[1]

Time point	Activity	Description of activities
Month 0	Phase 0 census (baseline)	In all 24 study VDCs, collect the following data: • Demographics • Ocular history screening (lifetime) • Bilateral photography of all participants
Month 6	Randomization	Randomize 12 VDCs to receive intervention and 12 VDCs to receive no intervention
	Intervention implementation	In 12 intervention VDCs, train FCHVs to: • Diagnose corneal abrasions • Provide antimicrobial ointments for abrasions • Refer when needed
Month 8	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 12	Phase 12 census	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening (past 12 months) • Symptom-based photography
Month 20	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 24	Phase 24 census	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening past 12 months) • Symptom-based photography
Month 32	Intervention awareness survey	In all 24 study VDCs, conduct a survey of a random sample of households to assess level of awareness of the intervention in both study arms
Month 36	Phase 36 census (final)	In all 24 study VDCs, collect the following data: • Demographics/vital statistics update • Ocular history screening (past 12 months) • Bilateral photography of all participants

[1]Census photograph grading and the 12-month visit began after the Month 12 census and continued on an ongoing basis

Table 2. Trial registration data and protocol summary

Data category	Information
Primary registry and trial identifying number	ClinicalTrials.gov NCT01969786
Date of registration in primary registry	October 25, 2013
Secondary identifying numbers	U10EY022880
Source(s) of monetary or material support	National Eye Institute-National Institutes of Health
Primary sponsor	National Eye Institute-National Institutes of Health
Secondary sponsor(s)	
Contact for queries	Thomas M Lietman, MD (tom.lietman@ucsf.edu)
Title	Village Integrated Eye Worker trial (VIEW)
Countries of recruitment	Nepal
Health condition(s) or problem(s) studied	Corneal ulcer prevention
Intervention(s)	Intervention: training volunteer community health workers to diagnose corneal abrasions and provide antimicrobial ointment to prevent corneal ulcers Control: no intervention
Key eligibility criteria	Community-level eligibility criteria (Village Development Committee): located within the catchment area of Bharatpur Eye Hospital, population ≥ 15,000 according to the 2001 national census Individual-level eligibility criteria: resident of eligible Village Development Committee
Study type	Cluster-randomized trial
Date of first enrollment	January 2014
Target sample size	24 Village Development Committees, 216,000 individuals
Recruitment status	Recruiting
Primary outcome(s)	Incidence of corneal ulcer (time frame: 3 years)
Key secondary outcomes	Trial-based cost-effectiveness analysis

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2, 12, 13
	2b	All items from the World Health Organization Trial Registration Data Set	15
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	13
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,13
	5b	Name and contact information for the trial sponsor	1,13
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	13
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	8-9, 11,12,13

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4
	6b	Explanation for choice of comparators	4
Objectives	7	Specific objectives or hypotheses	5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	6-7
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5, 7-10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	6
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	6
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	6
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	6
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	6
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	7-10
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	7-10

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	7-10
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11-12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11-12
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11-12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10-11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	2,12,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	12

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	7-10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	13
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	12
	31b	Authorship eligibility guidelines and any intended use of professional writers	13
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.