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Cluster-randomised trial of community-based screening for eye disease in adults in Nepal: the Village-Integrated Eye Worker Trial II (VIEW II) trial protocol

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ABSTRACT

Introduction The majority of blindness worldwide could be prevented or reversed with early diagnosis and treatment, yet identifying at-risk and prevalent cases of eye disease and linking them with care remain important obstacles to addressing this burden. Leading causes of blindness like glaucoma, diabetic retinopathy and age-related macular degeneration have detectable early asymptomatic phases and can cause irreversible vision loss. Mass screening for such diseases could reduce visual impairment at the population level.

Methods and analysis This protocol describes a parallel-group cluster-randomised trial designed to determine whether community-based screening for glaucoma, diabetic retinopathy and age-related macular degeneration reduces population-level visual impairment in Nepal. A door-to-door population census is conducted in all study communities. All adults aged ≥60 years have visual acuity tested at the census visit, and those meeting referral criteria are referred to a local eye care facility for further diagnosis and management. Communities are subsequently randomised to a community-based screening programme or to no additional intervention. The intervention consists of a single round of screening including intraocular pressure and optical coherence tomography assessment of all adults ≥60 years old with enhanced linkage to care for participants meeting referral criteria. Four years after implementation of the intervention, masked outcome assessors conduct a repeat census to collect data on the primary outcome, visual acuity. Individuals with incident visual impairment receive a comprehensive ophthalmological examination to determine the cause of visual impairment. Outcomes are compared by treatment arm according to the originally assigned intervention.

Ethics and dissemination The trial has received ethical approval from the University of California San Francisco Institutional Review Board, Nepal Netra Jyoti Sangh and the Nepal Health Research Council. Results of this trial will be disseminated through publication in peer-reviewed journals and presentation at local and international meetings.

Trial registration number NCT03752840

Strengths and limitations of this study

- The Village-Integrated Eye Worker Trial II is able to isolate the impact of screening for glaucoma, diabetic retinopathy and age-related macular degeneration by identifying cases of cataract and refractive error identically in both study arms.
- While poor visual outcomes due to glaucoma, diabetic retinopathy and age-related macular degeneration are relatively uncommon among the general population, the trial is able to detect a modest effect of the intervention by studying a large population with a high burden of blindness in Nepal.
- Screening staff and participants are unable to be masked due to the nature of the intervention although the primary visual outcome is collected by masked study personnel.
- Visual field testing will not be performed at a mass scale during the final outcome assessment, meaning that participants with good visual acuity but visual field loss will not be identified.
- The generalisability of the study to areas with better access to eye care services or different causes of blindness is uncertain.

INTRODUCTION

After cataract and uncorrected refractive error, the leading causes of visual impairment globally are glaucoma, diabetic retinopathy (DR), corneal opacity and age-related macular degeneration (AMD).[1] Glaucoma, DR and AMD may lend themselves to mass screening since these diseases are initially asymptomatic and each has an effective treatment.[2] However, challenges to screening exist. A simple diagnostic test that captures all conditions with high sensitivity and specificity is not currently available and thresholds for defining clinically meaningful disease are not established, most notably for glaucoma.[3] As has been noted by surveys using the rapid

assessment of avoidable blindness DR screening module, existing screening tests are generally expensive, difficult to transport and require some level of expertise to administer.[4] Thus while screening for eye disease in an individual patient intuitively should be effective, the efficacy and cost-effectiveness of mass screening for eye disease is uncertain.[5–7]

Several randomised controlled trials have been unable to demonstrate a benefit from programmatic vision screening of adults, but the available evidence is largely from resource-rich settings and the existing studies have in general been limited by small sample sizes, low intervention uptake, considerable loss to follow-up and the use of self-reported primary outcomes.[8–11] The Village-Integrated Eye Worker Trial II (VIEW II) is a cluster-randomised trial set in Nepal that uses the latest technology to screen for multiple eye diseases while addressing several limitations of prior studies.

METHODS AND ANALYSIS

Design overview and aims

The first Village-Integrated Eye Worker Trial (VIEW I) was a cluster-randomised trial conducted from 2014 to 2017 in communities near Bharatpur, Nepal, that was designed to assess the effectiveness of a community-based corneal ulcer prevention programme (ClinicalTrials.gov NCT01969786). VIEW II, an ongoing trial which started on 21 April 2019, builds off the infrastructure developed for that trial, but assesses the effectiveness of a programme designed to prevent blindness due to non-communicable eye diseases. This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials reporting guidelines.[12 13]

VIEW II is a parallel-group cluster-randomised trial designed to determine the efficacy of mass screening for glaucoma, DR and AMD in adults ≥60 years (online supplemental table 1). All study clusters receive visual acuity testing at baseline and then half are randomised to a screening intervention and the other half to no further intervention. The screening programme consists of intraocular pressure (IOP) measurement, optical coherence tomography (OCT) imaging and enhanced linkage to care. A door-to-door census with visual acuity testing of all individuals ≥60 years is conducted at baseline and at 4 years in all study clusters by masked field staff. The trial seeks to determine whether screening for glaucoma, DR and AMD reduces both all-cause and cause-specific visual impairment in adults ≥60 years at 4 years. Specific aim 1 hypothesises that individuals from clusters randomised to the screening programme will have better visual acuity compared with those receiving visual acuity testing alone, and specific aim 2 hypothesises that incident visual impairment due to glaucoma, DR and AMD will be less common in clusters randomised to the screening programme. The trial flow is depicted in figure 1.

The design of this trial addresses several challenges involved in studying population-based screening. First, a community-based screening programme focused on glaucoma, DR and AMD could also inadvertently identify cases of cataract and refractive error. Because cataract and refractive error are common and treatable, discovering cases of these conditions could lead to improved visual acuity outcomes regardless of whether the screening programme succeeded in identifying cases of glaucoma, DR or AMD. Thus, if the final visual acuity comparison indicated improved vision outcomes in the intervention arm, it would be unclear whether that improvement was due to screening of glaucoma, DR and AMD, or to case detection of cataract and refractive error. This is an important distinction given the cost and complexity of incorporating tests for glaucoma, DR and AMD into an eye outreach programme. To address this challenge, this trial offers visual acuity testing to all study communities at the baseline census (ie, before randomisation) and prohibits any visual acuity or refractive error testing in the screening programme. All adults with visual impairment at the baseline census are referred and have the opportunity for subsidised cataract surgery and refractive error correction. Because case detection of cataract and refractive error is conducted identically in both arms, the trial specifically isolates the impact of screening for glaucoma, DR and AMD. Second, progression of glaucoma, DR and AMD is relatively slow and poor visual outcomes are relatively uncommon, so a study would need to be large enough and of a long enough duration to have the power to detect a difference in outcomes. Although the realities of grant funding make it difficult to plan a study with many years of follow-up, this trial makes up for a relatively short 4-year follow-up period by enrolling a large number of participants in an area with a high burden of blindness, increasing the chances of detecting a modest effect of the screening intervention on this rare event. Third, simply identifying cases will not improve visual acuity. To ensure cases access appropriate care, the intervention includes enhanced linkage to care in which the study team actively follows and communicates with all cases identified from the screening intervention. Fourth, this trial uses an objective measurement of the primary outcome, assessed by masked data collectors to reduce the possibility of bias present in prior studies.

Participants

Study setting

This study takes place in periurban communities in the Chitwan and Nawalpur districts in Nepal. Study communities belong to the catchment area of Bharatpur Eye Hospital (BEH). A 2016 population-based survey in the study area estimated a 3.7% prevalence of severe visual impairment or blindness among individuals ≥50 years of age, with the most common causes being cataract

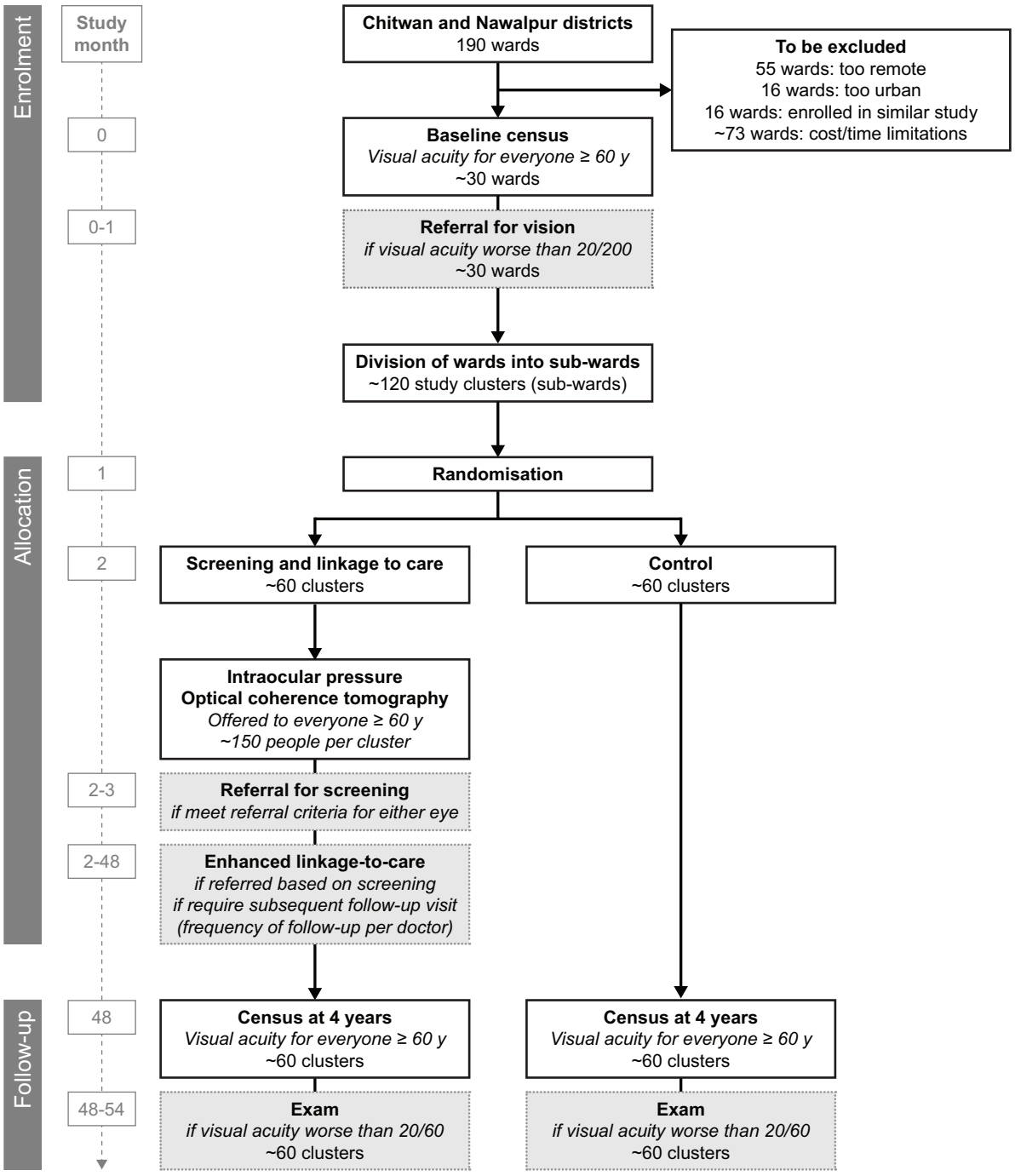

Figure 1 Trial flow and timeline. The randomisation unit is a group of contiguous small government demographic units (ie, toles) from the same ward, termed a study cluster. Wards are divided into study clusters after the initial census depending on the ward population; sample size calculations are approximations since baseline census activities are ongoing.

(76.2%), refractive error (6.9%), corneal opacity (3.0%), glaucoma (2.5%), AMD (2.5%), DR (1.5%) and other posterior segment disease (4.0%).[14]

Eligibility criteria

In this area of Nepal, districts are subdivided into municipalities, then wards, then toles. The randomisation unit for this trial (hereafter referred to as a cluster) is defined as a contiguous group of toles, with borders of clusters defined arbitrarily within each ward after the baseline census to target a population of approximately 400 households per cluster. Inclusion criteria for clusters include location in the Chitwan or Nawalpur district and accessibility by a vehicle not equipped with four-wheel drive, and for individuals the inclusion criterion is age ≥60 years, chosen because the relatively high rates of glaucoma, DR and AMD among this age group increase statistical power and reduce the required sample size.[15–17] No communities or individuals are excluded aside from those who refuse to participate; willingness to participate at the cluster level is elicited from District Public Health Offices prior to the start of the study.

Interventions

Baseline census

Census overview

Participants are recruited during a door-to-door census in all communities, performed before randomisation by a team of approximately 25 trained census workers. Visual acuity testing is performed for all residents ≥60 years of age, and those with visual acuity worse than 20/200 are referred for an eye examination; this threshold is based on local cataract surgery practice patterns. Verbal consent is obtained from the head of household and includes census activities and referral visits if indicated. Census data are collected in a custom-built mobile application (Conexus, Los Gatos, CA). After the census and visual acuity testing is complete and referral slips have been provided to eligible participants, the cluster is randomised to receive the screening programme or to no additional intervention.

Visual acuity testing

All participants ≥60 years old undergo visual acuity screening with the Peek Acuity mobile application (Peek Vision, Hertfordshire, England), which has been shown to be a reliable and valid method of assessing visual acuity in resource-limited settings.[18] Presenting and pinhole visual acuity are assessed for each eye at a distance of 2 m using the tumbling E optotype with the contralateral eye occluded. As per WHO recommendations, presenting vision is assessed with currently available refractive correction, if any.[19] Pinhole visual acuity is then assessed using the Lorgnette pinhole occluder. For both presenting and pinhole acuity, participants unable to read at a distance of 2 m are retested with tumbling Es at 1 m. Those unable to read at 1 m have low vision testing performed with Peek Acuity at 30 cm. The software records all data in logMAR units, with 1.8, 2.5, 3.0 and 4.0 assigned for counting fingers, hand motion, light perception and no light perception, respectively. Near visual acuity is not measured or treated since differential cointerventions based on presbyopia would not be expected to impact the trial outcomes. Interoperator reliability is assessed during the trial in a random sample of participants who receive a second Peek assessment by a different worker masked to the original result. Participants who meet referral criteria receive a referral slip that provides a free eye examination at their local primary eye care centre or BEH; cataract surgeries and spectacles are subsidised (table 1).

Screening and linkage-to-care intervention

Screening visit overview

In communities randomised to the screening intervention, all individuals aged ≥60 years are invited to a screening visit for IOP assessment and OCT imaging of the optic nerve, macula and anterior chamber angle. A single round of screening tests is conducted in a central location in each intervention cluster by a team of two trained ophthalmic assistants (ie, an allied health professional

Table 1 Referral criteria for the interventions and outcome assessment for the Village-Integrated Eye Worker Trial II

	Referral criteria	
Tests	Bharatpur Eye Hospital	Primary eye care centre
Baseline census		
Visual acuity	► Pinhole VA worse than Snellen 20/200	► Presenting VA worse than Snellen 20/200 and pinhole VA better than Snellen 20/200
Screening intervention		
OCT—angle	► AOD500 <0.17 µm ► AOD750 <0.25 µm ► TISA500 <0.07 µm ► TISA750 <0.13 µm ► SSA <18°	
OCT—macula	► Any intraretinal haemorrhages ► Macular oedema ► Many intermediate or ≥1 large druse ► Geographic atrophy ► Choroidal neovascularisation	
OCT—RNFL	► Abnormal (ie, red) superior or inferior average thickness on the automatic RNFL summary	
Intraocular pressure	► IOP ≥23 mm Hg in either eye	

AOD, angle opening distance (measured at either 500 or 750 µm); IOP, intraocular pressure; OCT, optical coherence tomography; RNFL, retinal nerve fibre layer; SSA, scleral spur angle; TISA, trabecular-iris space area (measured at either 500 or 750 µm); VA, visual acuity.

in Nepal). Ophthalmic assistants are trained to conduct and interpret OCT and IOP examinations prior to the start of screening and receive refresher trainings each quarter while screening is ongoing. No other testing is performed, and visual acuity is specifically discouraged in order to separate census activities, which occur in all communities, from screening activities, which occur only in the intervention communities.

All residents ≥60 years enumerated on the census are invited to participate via home visit by local mobilisers. Information about the screening visit is intentionally not posted publicly in order to reduce contamination. When a participant presents for screening, the screening team confirms eligibility and obtains written informed consent with a signature or thumbprint. Tests are performed on both eyes, with the right eye tested first.

IOP testing

IOP is measured with an iCare ic100 tonometer. Participants with an IOP ≥23 mm Hg are referred to BEH.

OCT imaging

OCT images are captured of the anterior chamber angle, macula and retinal nerve fibre layer (RNFL) using a Zeiss Cirrus 4000 OCT with the Anterior Segment Premier Module. An HD Angle scan is assessed for the angle opening distance at 500 and 750 µm, the trabecular-iris space area at 500 and 750 µm and the scleral spur angle using the manufacturer's software. A Macular Cube 512×128 scan is assessed qualitatively using the en face analysis for abnormal foveal architecture, intraretinal haemorrhages, macular oedema, drusen, geographic atrophy and choroidal neovascularisation. An Optic Disc Cube 200×200 scan is assessed with the manufacturer's optic nerve head and RNFL analysis, with documentation of the superior and inferior quadrant average RNFL thickness in microns as well as the classification relative to the manufacturer's normative data—that is, green (<95%), yellow (<5%) or red (<1%). Participants meeting at least one of the criteria presented in table 1 are referred. Of note, inability to capture a high-quality OCT image—usually due to media opacity—is not a referable condition. The frequency of ungradable images is minimised by referring participants with poor vision at the baseline census, allowing cataract extraction to occur prior to the screening visit. OCT is implemented since it allows detection of both anterior (ie, anterior chamber angle) and posterior (ie, glaucoma, DR and AMD) pathology with a single device; OCT may miss mild forms of disease that a fundus photograph might capture (eg, microaneurysms), but such mild disease would generally not be treated by an ophthalmologist anyway.

Referral visit

Any participant who meets referral criteria receives a paper referral slip to BEH at the time of screening. The participant is asked to present for an ophthalmological examination within the next 2 weeks—with the exception of those participants with IOP ≥40 mm Hg, who are offered free transportation to BEH on the same day of screening. The referral slip covers all registration fees of the referral visit and provides a subsidy for transportation, diagnostic tests, surgeries, laser procedures, intraocular injections and spectacles. Additional tests and procedures may also be subsidised. Referred participants undergo the following tests at BEH in a standardised fashion as part of BEH standard of care: visual acuity, refraction, slit lamp examination, gonioscopy, IOP and dilated fundus examination. Ancillary testing (eg, Humphrey visual field, fluorescein angiography, OCT) is performed as per the clinical judgement of the examiner.

An ophthalmologist reviews all clinical information together for both eyes and determines the main cause of visual impairment for each eye based on their clinical experience. If the examiner diagnoses a participant with an eye disease, a treatment plan is instituted. The design acknowledges the complexity of diagnosing and treating the targeted conditions; guidelines are provided but the diagnosis and treatment plan are individualised to the patient at the discretion of the ophthalmologist (online supplementary file 1).

Enhanced linkage to care

The study team tracks referred participants to ensure they complete their visit. If the participant does not complete their appointment within 2 weeks of referral, a team member calls the participant. A study vehicle is dispatched to study clusters approximately 1–2 months following the screening visit to offer free transportation for those who have not yet come to the referral appointment. The study team monitors participants requiring chronic treatment. Participants who do not make their appointment within the time frame for follow-up care suggested by the treating ophthalmologist are called with a reminder.

Four-year census

A repeat census is conducted in all clusters 4 years after implementation of the screening intervention. Census workers update vital status and demographic data collected at baseline and add all new community members. Visual acuity is assessed for all participants ≥60 years old following the same procedures employed at baseline. Participants who have pinhole visual acuity worse than logMAR 0.48 (Snellen equivalent 20/60) in either eye at the time of the final census are offered an eye examination consisting of refraction, IOP assessment, visual field assessment and anterior and posterior segment visualisation, performed by a clinician masked to treatment assignment. The 20/60 visual acuity threshold maximises the chances of detecting one of the eye diseases of interest while also limiting the total number of participants requiring an examination, hence reducing the costs of the study. It was decided not to pursue mass visual field testing at the 4-year census due to logistical challenges and also because of the lack of an optimal portable visual field test.

Table 2 Prespecified primary and secondary outcomes of the Village-Integrated Eye Worker Trial II, assessed at 4 years

Outcome	Note
Primary	
Pinhole visual acuity	► Measured in logMAR units separately for each eye with the Peek mobile application and a Lorgnette pinhole occluder. Peek measures logMAR visual acuity on a discrete 45-level scale from −0.3 to 4.0.
Secondary	
Cause-specific visual impairment	► Pinhole acuity worse than logMAR 0.48 (Snellen equivalent 20/60) due to glaucoma, diabetic retinopathy or age-related macular degeneration, as determined by standardised eye examination.
Bilateral blindness	► Pinhole Peek Acuity worse than logMAR 1.3 (Snellen equivalent, 20/400) in the better seeing eye.
Presenting visual acuity	► Measured in logMAR units separately for each eye with the Peek mobile application and currently available refractive correction, if any.[19]
Cost-effectiveness	► Costs per case of visual impairment prevented, with costs enumerated from a hospital perspective and visual impairment assessed from the final census.

Outcomes

Primary outcomes

The primary outcome for specific aim 1 is logMAR pinhole visual acuity in each eye as assessed by the Peek mobile application at the final census, regardless of eye condition. The primary outcome for specific aim 2 is eye-level incident visual impairment due to the eye diseases targeted by the screening intervention (ie, glaucoma, DR or AMD), defined as a Peek pinhole acuity worse than logMAR 0.48 at the 4-year census and logMAR 0.48 or better at the baseline census, with cause assessed at the eye examination following the final census. Secondary outcomes are listed in table 2. While the ideal outcome would be best spectacle-corrected visual acuity, this would be difficult to implement; pinhole acuity provides a reasonable although imperfect approximation.[20]

Participant timeline

The timing of enrolment, randomisation and follow-up visits is shown in figure 1.

Assignment of interventions

Randomisation

Allocation occurs at the cluster level. Clusters are randomised in a 1:1 ratio either to baseline visual acuity testing plus the screening programme or to baseline visual acuity testing alone. The randomisation sequence is generated by the trial biostatistician at the University of California, San Francisco in R (R Foundation for Statistical Computing, Austria, Vienna); block randomisation is employed with permuted blocks of 6, 8 and 10 to ensure balance. The randomisation sequence is uploaded to the Research Electronic Data Capture (REDCap) randomisation module and a study coordinator randomises each study cluster after the census is complete for that cluster.[21] Concealment of allocation is ensured at the cluster level by performing randomisation after the baseline census is completed and at the individual level by offering the intervention to all community members ≥60 years of age. Study staff from BEH are responsible for implementation of the randomisation sequence.

Masking

Given the nature of the intervention, study personnel responsible for implementing the screening intervention are not masked to allocation. Census workers for the final census are not informed about the study hypotheses or the randomisation assignment. Differential cointerventions in the two treatment arms are possible. Most notably, it is possible that the increased attention provided during screening visits will make participants in the screening arm more likely to visit an eye care provider and receive treatment for an eye condition, independent of the actual screening test results. Such a scenario is mitigated by providing visual acuity screening for both arms identically and before randomisation, with referrals and cataract surgeries subsidised by the trial.

Selection bias and contamination

In the intervention clusters, screening is offered to individuals ≥60 years based on the baseline census. However, it is likely that the census will not capture all individuals ≥60 years, since some people may be absent at the time of the census or may subsequently move in to the community. It is possible that some community members not on the cluster's census list will nonetheless seek out screening. Allowing such individuals to be enrolled in the trial could bias the result since the control arm does not have an analogous opportunity to enrol such participants (ie, selection bias). Moreover, it is possible that some of these individuals actually reside in a control cluster but misstate their community of residence in order to receive screening services (ie, contamination). While one solution for these sources of bias would be to turn away anyone not captured at the initial census, such an approach could create ill will towards the screening programme. Thus, persons presenting for screening who are not on the cluster's census list will be screened if the mobiliser or

other community members confirm the person indeed lives in the community. However, any such individuals added after the baseline census will not be included in the primary analyses in order to prevent bias.

Data collection, management, analysis

Data collection

Census and screening data are collected electronically using a custom-made mobile application on mobile devices and uploaded daily onto a secure, password-protected, central server on Salesforce.com. Peek Acuity is integrated into the mobile application. Data collected during referral and follow-up visits are collected and managed using REDCap electronic data capture tools hosted at the University of California, San Francisco.[21]

Quality control

OCT images that trigger a referral and a random sample of negative OCT images are reviewed by a BEH optometrist or ophthalmologist. Discrepancies between the original and quality control interpretations are communicated to the field staff.

Data management

Supervisors at BEH oversee data collection through regular visits to study team members to ensure quality, completeness and adherence to standardised data collection procedures. Data collection progress is monitored daily by study coordinators at BEH with the help of custom dashboards on the Salesforce.com platform. Data quality is monitored weekly by analysts at the University of California, San Francisco, and discrepancies and missing data communicated to the study team at BEH for resolution.

Statistical methods

Sample size

For simplicity, sample size calculations assume analysis of a single eye per participant. In reality, both eyes will be included, providing marginally higher power. Assumptions are based on pilot studies in Nepal and trials of infectious keratitis in India.[22] We estimate that 120 clusters (60 per arm) will provide greater than 80% power to detect a one-letter difference in visual acuity, assuming 150 individuals ≥60 years per 400-household cluster, a baseline mean visual acuity of 0.26 logMAR (SD 0.52), an intraclass correlation coefficient of 0.004, a correlation of 0.8 between baseline and follow-up visual acuity values, 33% loss to follow-up at the individual level and no loss to follow-up at the cluster level.

Specific aim 1 analysis

The unit of analysis is the eye. The analysis population includes those individuals aged ≥60 years at the baseline census who had visual acuity assessed during the census. logMAR pinhole acuity at 4 years is modelled as a function of treatment allocation and baseline logMAR acuity, statistically adjusting for correlation of data of eyes from the same person and people from the same community.

Specific aim 2 analysis

The unit of analysis is the eye. The analysis data set, drawn from individuals aged ≥60 years at the baseline census, consists of eyes without visual impairment at baseline (ie, logMAR acuity ≤0.48). Incident cases of visual impairment caused by glaucoma, DR and AMD are grouped together into a composite outcome and modelled with negative binomial regression, using time since baseline as an offset and statistically adjusting for correlation of data of eyes from the same person.

Analysis of secondary outcomes

Secondary vision outcomes will be modelled in regression models that account for cluster-correlated data at the community level and person level.

Significance testing

Monte Carlo permutation testing will be performed to compute the p values for the primary and secondary analyses (10 000 replications, accounting for block randomisation).

Monitoring

Data monitoring, harms, auditing

Data and Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) meets in person annually and by phone as needed. The DSMC reviews the study protocol and major modifications before implementation and monitors participant safety. The design precludes the use of futility stopping rules or interim efficacy analyses. However, early termination due to inadequate implementation of the baseline intervention, as assessed by process indicators, may be considered by the DSMC.

Adverse events

The screening tests employed by this study are non-invasive, low-risk, standard-of-care diagnostics. The main ocular adverse event is corneal abrasion during IOP assessment. Adverse events are documented at the time of the census or screening in the mobile application and also communicated verbally to study staff at BEH. Adverse event data are reviewed by the DSMC.

More detail regarding data management, monitoring and analysis can be found in the Manual of Procedures and Statistical Analysis Plan (https://osf.io/fgvrt/).

Patient and public involvement

The study design and methods were informed by participant contributions to the VIEW I as well as an exploratory trial that allowed refinement of the study activities in VIEW II. Both of these studies employed participant focus groups to better understand how participants use local eye health resources. The knowledge gained from these focus groups guided the development of the enhanced linkage to care programme incorporated into the VIEW II intervention as well as the use of local mobilisers to advertise the screening intervention.

ETHICS AND DISSEMINATION

Ethical approval

The University of California San Francisco Institutional Review Board, Nepal Health Research Council and Nepal Netra Jyoti Sangh provided ethical approval for the trial. Protocol modifications are approved by these institutions prior to implementation.

Data availability statement

Deidentified data will be shared with other investigators upon request after the conclusion of the study. A request form will be available on Open Science Framework (https://osf.io/fgvrt/); all requests will be approved by the executive committee of the trial before sharing the data.

Dissemination policy

The results of this trial will be presented at local and international meetings and submitted to peer-reviewed journals for publication. The principal investigator will lead the writing committees for primary and secondary analyses and follow the International Committee of Medical Journal Editors when deciding authorship eligibility. Investigators who have contributed to the research but not met authorship criteria will be included in the acknowledgements section of the manuscript. No professional writers will be employed. The complete Manual of Procedures and Statistical Analysis Plan has been published in the Open Science Framework repository and is publicly available (https://osf.io/fgvrt/).

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Contributors JDK, KSO and VMS contributed to study design and implementation as well as writing of the manuscript. GB, SB, RPK, RB, JSM, TCP and TML were involved in study design and implementation as well as editing the manuscript.

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Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The study sponsors had no role in study design, data collection, data management, data analysis, data interpretation, manuscript writing, or the decision to submit the report for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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