Protocol for a platform trial of intended service user-derived interventions to equitably reduce non-attendance in eye screening programmes in Botswana, India, Kenya & Nepal

Abstract

Background

Major community-based eye screening programmes are running in Botswana, India, Kenya, and Nepal with the aim of promoting eye health for all. Preliminary data suggest that only 30-50% of those who screen positive and are referred then access further eye care. The access rate is even lower for certain population groups. This platform trial aims to test multiple, iterative, public health interventions and simple service modifications with a series of individual randomised controlled trials (RCT) conducted in each country, with the aim of increasing the proportion of people attending from left-behind groups.

Methods

This platform trial protocol sets the population, outcome, and statistical approach that will be used to run a series of individual RCTs that each test different interventions – as yet undefined – that will be developed based on the suggestions of intended service users in a series of related qualitative studies. In each setting the population will be people found to have an eye health need at screening and referred to the local triage clinic. The primary outcome will be the proportion of people from the population group with the worst attendance at baseline who attend triage clinic. Our secondary analysis will examine overall mean attendance across all groups. We will run serial RCTs in each country, each testing different interventions against a control. We will allow cluster and individual RCTs. For interventions delivered to individuals, we will calculate Bayesian posterior probabilities of attendance in each arm every 24 hours. Each RCT will continually recruit participants until the following default stopping rules have been met: there is a >95% probability that one arm is best; there is a >95% probability that the difference between the arms remaining in the trial is <1%; or 10,000 people have been recruited. Lower thresholds may be used for RCTs testing interventions with very low risks and costs. The specific design of cluster RCTs will be determined by our research team once the intervention is known, but the population group and outcome will be the same. When the proportion of people attending exceeds 80% in all population groups, we will end the platform trial in that setting i.e. no further individual RCTs will be run.

Discussion

We will set up a platform trial in each country to govern the running of a series of pragmatic, embedded, parallel, multi-arm, superiority RCTs to test a series of service modifications suggested by

non-attenders. The aim is to identify serial marginal gains that cumulatively result in large improvements in attendance and improve equity.

Keywords

Health services research, platform trial, embedded trial, global health, mHealth, equity

1. Reporting guidelines

This protocol has been prepared in line with the SPIRIT checklist[1] and incorporates relevant elements from the CONSORT[2] extensions for equity-oriented[3] and pragmatic[4] trials.

2. Trial registration

International Standard Registered Clinical/soCial sTudy Number (ISRCTN): xxxxxx

3. Protocol version

13/07/2023

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5. Roles and responsibilities

5a. Protocol contributors

- Dr Luke Allen, Principal Investigator, LSHTM, luke.allen@lshtm.ac.uk
- Min Kim, Co-Investigator, min.kim@lshtm.ac.uk, LSHTM,
- Prof Oathokwa Nkomazana, Co-Co-Principal Investigator, University of Botswana
- Dr Michael Gichangi, Co-Co-Principal Investigator, gichangi58@yahoo.com, LSHTM and Kenyan Ministry of Health
- Sailesh Kumar Mishra, Co-Co-Principal Investigator
- Shalinder Sabherwal, Co-Co-Principal Investigator
- Dr David Macleod, Co-Investigator and statistician, david.macleod@lshtm.ac.uk, LSHTM
- Prof James Carpenter, Co-investigator, LSHTM and UCL
- Dr Malebogo Tlhajoane, Co-investigator, malebogo.tlhajoane@lshtm.ac.uk, LSHTM
- Mr Ari Ho-Foster, Co-investigator, University of Botswana
- Bakgaki Ratshaa, Co-Investigator, University of Botswana
- Dr Nigel Bolster, Co-Investigator, shnb12@lshtm.ac.uk, LSHTM,
- Dr Jacqui Ramke, Co-Investigator, LSHTM
- Prof Matthew Burton, Co-Investigator, matthew.burton@lshtm.ac.uk, LSHTM
- Prof Andrew Bastawrous, Chief Investigator, LSHTM

5b. Trial sponsor

London School of Hygiene & Tropical Medicine, WC1E 7HT, UK, Tel: +44 207 927 2626, RGIO@lshtm.ac.uk.

5c. Role of sponsor and funders

The study sponsor and funders will not have any role in- or ultimate authority over the study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

5d. Team composition

	Coordinating centre	Trial Steering Committee	Data management team
1.	Luke Allen	James Carpenter (chair)	Nigel Bolster
2.	Malebogo Tlhajoane	Malebogo Tlhajoane	Malebogo Tlhajoane
3.	Bakgaki Ratshaa	David Macleod	David Macleod
4.	Sarah Karanja	Luke Allen	Min Kim
5.	Sailesh Kumar Mishra	Min Kim	Luke Allen
6.	Shalinder Sabherwal	Oathokwa Nkomazana	
7.	Hannah Chroston	Michael Gichangi	
8.		Sailesh Kumar Mishra	
9.		Shalinder Sabherwal	
10.		Nigel Bolster	
11.		Matthew Burton	
12.		Andrew Bastawrous	

Introduction

This protocol sets out the approach for running platform trials in four countries that will test interventions suggested by local intended service beneficiaries with the intention of improving equitable access to community-based eye services. Table 1 sets out the definitions of common terms used in the protocol and Figure 1 illustrates how arms, interventions, individual trials and the overarching platform interrelate.

Table 1: Terms used in this protocol	
Access and attendance	We are interested in **access to services**, which is driven by complex supply and demand factors. We will use **attendance** as the primary indicator of access. We note that access and attendance are both proximal outcomes in that they do not automatically lead to the receipt of good quality care and improved health outcomes.

Eye care need	We are concerned with whether those with an **eye care need** access services. This includes near or distance vision impairment and non-visually impairing eye conditions, included but not limited to: uncorrected / under-corrected refractive errors, cataract, a red eye, eye discomfort or pain, or any other eye-related issue identified by screeners.
Left behind population groups	We focus on the **population groups** with the worst access to services, aligning with the UN Agenda for Sustainable Development's "central, transformative promise" to 'leave no one behind' and 'reach the furthest behind first'. Further UN guidance states that "leaving no one behind means moving beyond assessing average and aggregate progress, towards ensuring progress for all population groups at a disaggregated level." The UN uses the terms 'worst-off' and 'left-behind' groups interchangeably.[5] Multiple population subgroups and domains can be used for disaggregation, such as age, sex, ethnicity, occupation, income, socioeconomic status etc. We use the terms 'subgroups' to describe sociodemographic variables (e.g. sex, ethnicity, religion), and 'domains' for socioeconomic variables (e.g. income, education, occupation).
Platform trial	Platform trials use shared infrastructure and a master protocol/overall set of rules to run multiple individual trials that test different interventions against a constant outcome (attendance) in the same target population (people identified with an eye need at screening and referred for further care).
Individual trial	A randomised controlled trial of a single intervention (e.g. vouchers or SMS reminder messages) that is performed under the platform trial protocol.
Intervention/ service modification	The thing that is being tested e.g. SMS reminder messages, vouchers, or different clinic opening times. We use the term '**intervention'** when a new element is added to programmes (such as vouchers), and '**service modification'** when an existing element is tweaked, such as amending opening hours, or the wording used in communication materials.
Arms	Variants or 'doses' of the intervention/service modification. These are tested against each other and a control arm. For instance, an individual trial might test vouchers (the intervention) with three different arms; $1, $5, and $10 against a control arm (no voucher).

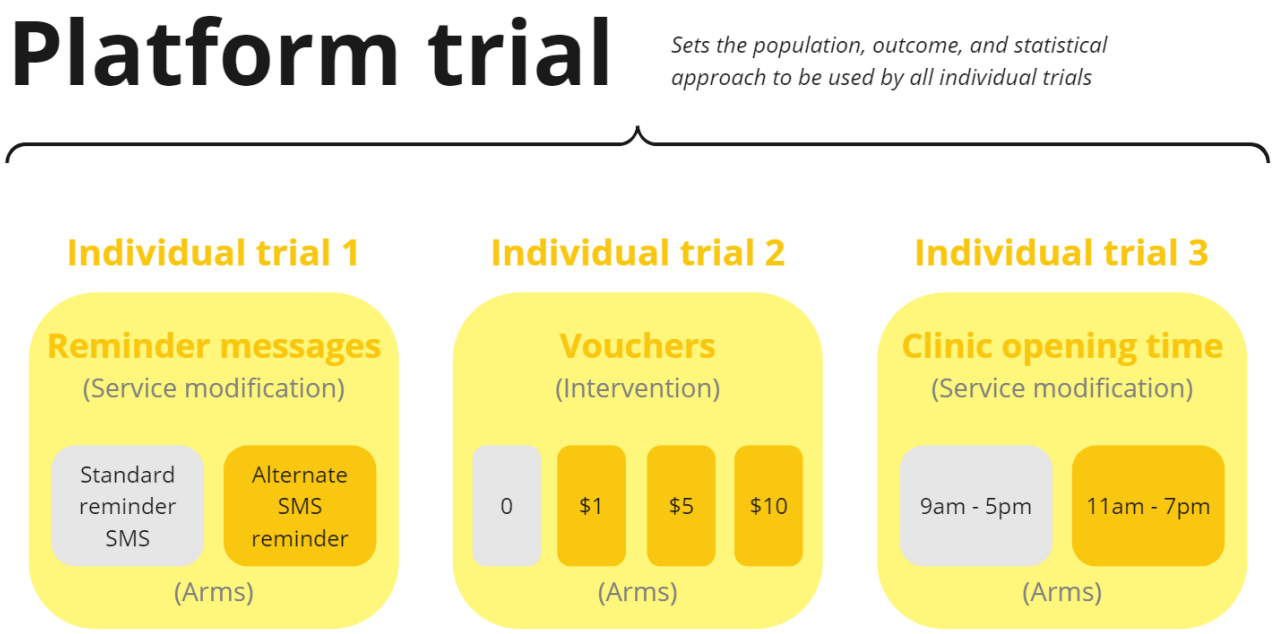

Figure 1: Three example individual trials that test service modifications/new interventions against the status quo (grey boxes) as part of an overall platform trial

6. Background and rationale

Many health programmes experience large mismatches between those identified with a clinical need and those who access services. A recent international systematic review of 'no-show' appointments across all medical specialities in primary and secondary care estimated that 23% of clinic appointments are not attended, with the highest rate observed on the African continent (43%).[6] Complex supply and demand factors govern access to health services,[7] and systematically marginalised populations are often the least likely to receive care.[8,9] Improving access to care lies at the heart of Universal Health Coverage (UHC) and is a core element in the Sustainable Development Agenda.[10]

Eye services offer an instructive case study. Approximately 1.1 billion people (over 10% of the global population) live with vision impairment that could be easily corrected.[11] Two very cost-effective interventions - spectacles and cataract surgery – could eliminate over 90% of all vision impairment worldwide. Although provision of these services has risen in recent decades, effective coverage rates exhibit marked socioeconomic gradients at the international and intra-national levels, for example, the global effective refractive coverage is reported at 36%, with high-income countries reporting 90% and low-income only 6%.[11]

In major eye screening programmes, once people have been identified with an eye need and referred on, only around 30-50% of these people access care, and research from Nigeria and Sri Lanka suggests that unmarried (primarily widowed) women and people living in rural areas are the least likely to access care.[12]

Our research collaborative (LSHTM, Peek Vision, COESCA, Kenyan MoH, University of Botswana, NNJS, Dr Shroff's Charity Eye Hospital) is working with four major eye screening programmes to identify the population groups least able to access care in each setting (Table 2).

Table 2. Eye screening programmes

Country	Programme description	Dates	Population
Botswana	The 'Pono Yame' national school-based programme. Screeners travel to every school in the country and refer positive cases to local triage and treatment camps	2022-2024	One national programme: 500,000 children aged 5-18y
India	House-to-house community-based screening in three sites in central Uttar Pradesh.	2023-2025	Three sites: each with 50,000 to 70,000 adults and children.
Kenya	Community-based screening programmes in Meru and Kwale with school-based and primary care facility-based screening.	2022-2025	Two sites with: each with approximately 1 million adults and children
Nepal	Regional primary care-based passive screening programme in Eastern Nepal.	2022-2023	One regional site with approximately xxx adults and children

Through interviewing representatives from the socioeconomic groups that experience the lowest attendance rates in a related qualitative research project, we aim to identify potential service modifications that could reduce the social gradient in attendance. Testing whether these intended service user-derived service modifications are causally associated with positive change requires the use of randomisation.

Randomised control trials (RCTs) provide the most robust means of appraising whether an intervention is causally associated with a change in a given outcome. Unfortunately, the resources and technical expertise required to run an RCT generally preclude their use by day-to-day health services. To overcome this barrier, we are proposing use of a semi-automated RCT platform embedded within web-based patient workflow screening and referral systems to perform elements of randomisation, allocation, outcome assessment, and statistical testing. Global health programmes constantly adapt in order to better meet the needs of their beneficiaries, however the impact of these adaptations is rarely assessed. By reducing the barriers for rigorously testing service

modifications, we hope to equip programme managers with the ability to run resource-light, real-time, embedded RCTs to continuously improve their programmes and address socioeconomic inequalities in attendance and outcomes.

Rather than running serial RCTs – each requiring lengthy set-up periods and very similar protocols, we intend to set up a platform trial. This design uses a master protocol to evaluate multiple interventions in the context of a single outcome in a perpetual manner. Platform trials are a form of multi-intervention, multi-stage design.[13]

Addressing inequitable service outcomes is likely to require multiple different modifications in the context of continuous improvement. Early data from Botswana suggests that approximately 1/10 schoolchildren have an unmet eye health need but less than a third attend community eye clinics for further assessment and/or treatment. In addition, early findings suggest that boys, children of immigrants, and those from families receiving social welfare may be the least likely to access referral appointments.

We intend to engage with representatives from groups that are facing the highest barriers to accessing care to explore their perceptions of the types of interventions and service modifications that could improve access. Our platform trial will be used to test the interventions suggested by these left behind groups.

7. Objectives

This platform trial will iteratively test a series of interventions selected with intended service beneficiaries to increase attendance rates in community-based eye screening programmes in Botswana, India, Kenya and Nepal. Each of these programmes use the mature and validated app-based screening system developed by Peek Vision – a LSHTM not-for-profit spin-out.[14–18] Programme managers in each country are interested in identifying incremental gains from multiple, small service modifications to deliver iterative improvements in attendance.

8. Trial design

This Bayesian, embedded, pragmatic, superiority, platform trial protocol will be used to evaluate multiple interventions against a control group, using a constant outcome. The same platform approach will be used in each setting, but the interventions will all be locally-derived and tested. In each setting, the platform trial will be embedded into the local eye screening programme, using referral and attendance data directly derived from the patient management and flow software in each setting.

9. Study setting

Platform trials will be established in regional and national community-based eye screening programmes in Botswana (national), Nepal (one regional site), Kenya (two regional sites), and India (three regional sites). All seven sites operate using integrated screening and patient management

software developed by Peek Vision. In each site our platform trial will use data routinely gathered using Peek software.

Peek Vision is a leading provider of eye screening software worldwide. The 'Peek Acuity' app is used to screen participants for vision impairment, to capture observations by screeners and health practitioners, and to gather demographic data, as well as linking participants to a referral system that tracks each of their progression through the local eye health system. The same app is used to collect data on visual acuity, socioeconomic status, referral status, and attendance status (our primary outcome). Our trial will use these routinely collected data to test whether a series of interventions are able to reduce the proportion of people from marginalised groups with an eye care need who do not attend triage clinic once referred (Figure 2).

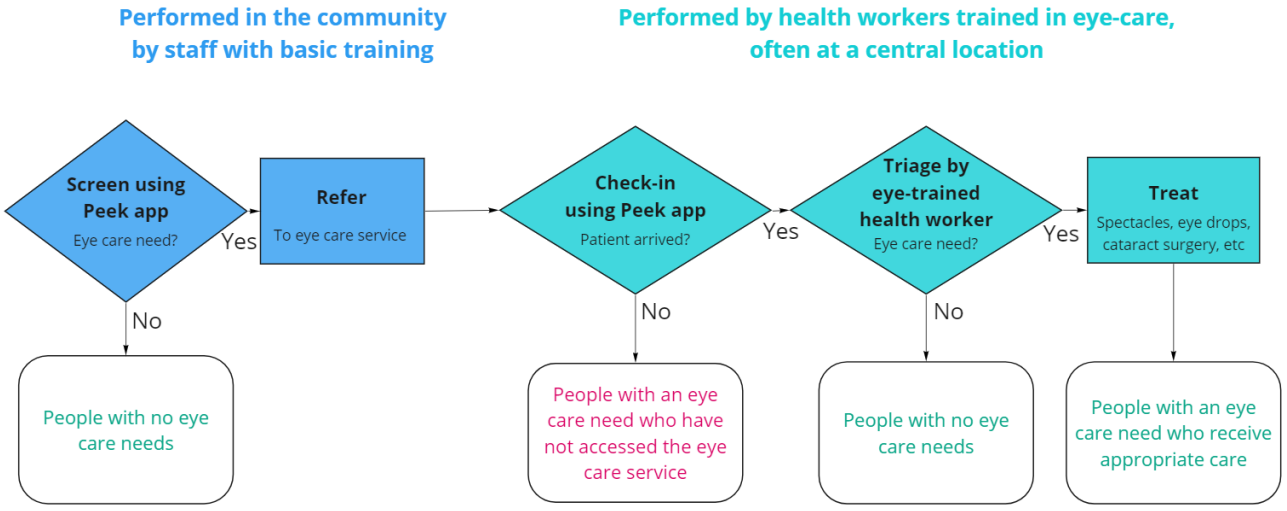

Figure 2: Schematic of patient flow through a Peek programme

10. Eligibility criteria

As a pragmatic trial, the eligibility criteria are determined by local programmes. We will include children aged over 5 years and adults who participate in Peek-powered eye screening programmes as outlined in Table 2. We will exclude those who do not meet local clinical service eligibility criteria, such as age (most programmes exclude children younger than 5 years).

11. Interventions

11a. Interventions and administration

This platform trial is being set up to test service modifications suggested by representatives of groups that face the highest barriers to receiving care. The intention is to continuously improve attendance rates with the greatest gains focused on left behind groups.

This platform trial forms the testing element of a broader continuous improvement model called 'IM-SEEN' (IMprovement Studies for Equitable and Evidence-based iNnovation). The model has already

been integrated into Peek programmes (orange boxes shown in Figure 3). In this continuous improvement approach, data collectors **gather** contact details and sociodemographic data from those found to have an eye problem prior to referring them. This means that programme managers using Peek have a complete record of who has not attended clinic on the appointed day, and they are able to **identify** the population group with the lowest attendance. Next, the programme leadership team can **engage** with representatives of left-behind groups to elicit barriers and identify potential service improvements that would reduce non-attendance – such as changing the clinic location or amending the wording of the SMS reminder messaging. The final step is to use embedded RCTs to **test** these proposed improvements with new referrals. Effective interventions will be adopted across the programme. Further information on the broader IM-SEEN approach has been published elsewhere.[19]

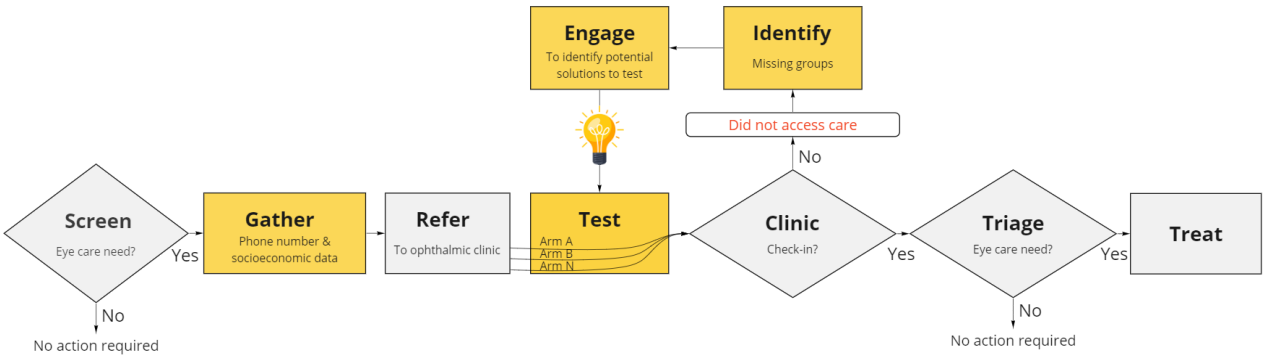

Figure 3: Elements in the IM-SEEN continuous improvement model

Screeners collect data on age, sex, location, language, ethnicity, health status, education, occupation, and income/assets, with minor local variations and enter these data into the Peek app directly after screening. Some of these categories are binary whereas other have multiple response options e.g. language. In all, the survey data can be used to divide screening populations into approximately 60 different groups, each defined by a single characteristic e.g. 'female' or 'primary school education'. We perform multivariable logistic regression to identify which population subgroups have the lowest attendance in each site. This is the 'identify' stage from Figure 3.

We then conduct interviews with members of the group with the lowest attendance to identify potential service modifications to improve attendance. Rather than designing de-novo interventions, or selecting complex interventions, the focus of this process is on identifying very simple service modifications such as changing the time, day, or location of clinics, changing the language or wording of reminder SMS messages, or providing simple incentives like vouchers. There is scope to identify other 'off-the-shelf' interventions that have previously been shown to work in other contexts, but the focus is firmly on translation and implementation research rather than discover or knowledge generation i.e., the platform trial will be used to run 'T3/T4' implementation studies in each site.[20]

Once the elicitation studies have generated a list of potential service modifications, a local management group comprised of community representatives, programme managers, public health experts and programme managers (Box 1) will select a shortlist of service modification that can be tested, based on the following criteria:

- Impact: is the intervention likely to improve attendance? i.e., has this intervention been tested in other contexts and demonstrated a meaningful effect?
- Risk: what level of risk does the intervention pose to service users?
- Feasibility: how easily can we implement the intervention?
- Cost: is the intervention affordable for the programme given existing budgetary constraints?

All interventions felt to present any more than minimal risk to participants will be excluded. An explicit trade-off discussion will be held around the maximum financial resources that can be released to fund the testing of one or more intervention (which carries an opportunity cost in terms of the number of people who can be screened) and the minimum 'meaningful' improvement that would be required to justify this expenditure. For instance, the local management group may be willing to screen 1% fewer people if attendance rates in the worst-off group improved by >5%. This decision directly informs the next step: agreeing the stopping rule thresholds for the trial ('x', 'y', and 'n' in the three rules below):

1. There is a >x% probability that one arm is best.
2. There is a >y% probability that the difference between the arms remaining in the trial is <1%.
3. A maximum of n people have been recruited.

The same three rules will be used for every trial, but the values of x, y and n will vary depending on the intervention. The management group will select the thresholds that are most appropriate for the given individual trial, guided by a statistician. The group may accept lower thresholds (and therefore higher risks of type I & II error) for trials of interventions with very low costs, risks, and implementation requirements. For instance, in testing two different versions of a SMS reminder message that are exactly the same cost, the group may use a 51% probability that one arm is best. In contrast, there is a greater imperative to minimise type I and II errors for costly or more risky interventions. The chosen thresholds and the intervention will be reviewed by an independent ethics committee for each individual trial.

We aim to test multiple intervention/service modifications over time in each site e.g. trialling different wording of SMS reminders, or different clinic opening hours, or vouchers of different values – and then take the most effective version to scale across the local programme before repeating the cycle to identify the next intervention/service modifications to test. Individual trials will end once the stopping rules are met. The overall platform trial will close once attendance exceeds 80% for all groups in that particular site.

Box 1: Programme management team

The platform trial infrastructure is being set up by the IM-SEEN collaborators, comprised of LSHTM, Peek Vision, COESCA, Kenyan MoH, University of Botswana, NNJS and Dr Shroff's Charity Eye Hospital using Wellcome Trust and NIHR funds, and in collaboration with national eye care administrators. Decisions around which interventions to test will be made by a multistakeholder group that includes the screening programme funders, implementing partners, and community representatives with support from LSHTM statisticians. Once the first few interventions have been tested, it is anticipated that the local programme management teams will assume total responsibility for the platform trial process in each country, led by the relevant national decision-makers with responsibility for funding and administering the screening programme in collaboration with local lay representatives and programme implementers. Our ultimate aim is that the broader IM-SEEN process of gathering sociodemographic data, engaging with left-behind groups, identifying interventions, and testing them can be taken to scale across many different sites and services, and that as the approach matures, an increasing number of decisions can be delegated from senior managers to local programme implementers.

Types of interventions

This platform trial will be used to test multiple interventions in series i.e. one after the other. It is likely that interventions will be identified that can be administered either at the individual or cluster level. Cluster trials are permitted under this platform trial. Cluster randomisation will be performed by the teams' statisticians with pairs of clusters matched by social, geographic, economic and demographic factors. Examples of cluster interventions may include local broadcasts to sensitise populations, new transport services to a given clinic, or changes to the opening times, languages, or locations of clinics.

Examples of individual-level interventions might include vouchers, changes to communication content, wording, timing, and modality (e.g. text message reminder messages), the use of differing visual acuity thresholds, or individual assistance with transport.

We envisage that the majority of interventions will be administered to every person who is referred. Our hope is that interventions will lead to a rise in overall attendance in addition to a (larger) rise in attendance among the left-behind population group. This outcome would support the broader goals of proportionate universalism whereby outcomes improve for all, with the greatest gains seen in those with the greatest baseline need.[21]

In some cases, the intervention recommended by the left-behind group and selected for testing may be 100% specific for that group – for instance providing SMS reminders in a new language. In this circumstance, we would not administer the intervention to every person who is referred. Rather, we will restrict that individual trial to the left-behind population group.

Some of these individual-level interventions are digital and could be administered by the Peek software directly after randomisation and allocation – for instance by sending different variants of an SMS reminder message, or an electronic voucher via SMS. Other individual-level interventions will require human involvement, such as giving out paper vouchers, or organising transport. Table 2 provides a matrix of example interventions.

Table 2: Examples of digital and non-digital interventions delivered at the individual and cluster levels

Type of intervention	Individual	Cluster
Digital	No human input required for intervention delivery. Peek software performs random allocation and delivers the intervention e.g. · SMS messages · Pre-recorded voice messages · Visual acuity thresholds · *eVouchers*	Humans select the clusters and the Peek software delivers interventions e.g. · SMS messages sent to a headteacher · Messages sent to a village chief · Pre-recorded voice messages sent to a primary care facility manager
Non-digital	Peek software performs random allocation then informs the human team. They deliver the interventions e.g. · Physical vouchers · Chaperones · Individualised transport assistance	Peek software can randomise the clusters, but humans need to deliver the interventions e.g. · Radio broadcasts · Training for implementers · New clinic times or locations · New bus services

Note that this trial will not test any pharmaceutical or medical interventions: the focus is on service modifications and public health interventions.

This platform trial offers the flexibility of being able to test a number of different interventions under the same master protocol i.e. always using the same population and primary outcomes. Each individual trial that takes place within the overall platform trial will have one or more arms (i.e. different variants/doses of individual interventions) tested against each other and a control. The investigators will not make any efforts to standardise interventions or their delivery as this is a pragmatic trial testing real-world delivery.

The local management group and screening programme funders will be responsible for obtaining the funding required for each intervention, using the resources available to their services. They will be

facilitated to apply for external grant funding to cover the costs of interventions where appropriate. We note that many potential interventions will only incur small marginal costs.

11b. Discontinuing or modifying interventions

Arms will be discontinued (or modified to remove the risk) if there is evidence that they are harming exposed individuals. We note that only low/negligible-risk service modifications will be tested. Risk will be assessed at the intervention selection stage by a group of researchers, programme managers and lay representatives. Interventions that are deemed to be appropriate will also be independently reviewed by independent ethics committees in each setting before they are implemented in the platform trial.

11c Adherence

There are no *a priori* strategies to improve adherence as we are not pre-specifying the interventions.

11d Concomitant interventions

As our trials will be embedded within routine service delivery, we cannot exclude the possibility that other initiatives will be introduced by local teams before, during, or after individual trials. We will report all programmatic changes that take place during individual trials that could bias our findings.

12. Outcomes

This platform trial focuses on testing interventions that improve equitable access to eye services among those identified with a need during screening. We will use attendance as a proxy for access. Our analysis focuses on the population groups found to have the lowest attendance at baseline.

Primary outcome: The proportion of people attending triage clinic on their appointed date from the left-behind group, measured using attendance data collected by staff when people check-in.

The left-behind group will be identified at baseline as part of the 'identify' stage of the IM-SEEN process. This group will be constituted of the group(s) with the lowest baseline attendance rates that collectively constitute at least 10% of the total population. A focus on left-behind groups is important to programme managers who are trying to close gaps, extend health service coverage, and ensure that their services do not exacerbate existing inequalities.

When referred participants check-in at ophthalmic clinics, their attendance status is recorded by administrative staff using the Peek app, which automatically updates a central database that holds records of each participant's eye care need, sociodemographic characteristics, arm allocation, and attendance status at the ophthalmic clinic on the appointed date. Our Bayesian algorithm will review the attendance data for every referred participant every 72 hours and calculate the probability of attendance within each arm. In our modelling we have estimated that 100 people will be referred every 72 hours. This aligns with what we have observed in India and Kenya where approximately 1,000 people are screened per day, of whom approximately 1/3 are referred. We have stipulated that the left-behind group will include at least 10% of the total population (i.e. 100 people every 72 hours).

Secondary outcome: The proportion of people attending triage clinic on their appointed date across the entire population, measured using attendance data collected by staff when people check-in.

If an intervention is found to increase attendance among the left-behind group, we also want to check whether there has been an impact on the overall mean attendance rate. This is to hedge against adopting an intervention that improves access for the left-behind group but leads to a large overall fall in attendance across the entire programme. We will use absolute percentage differences in attendance for comparisons between the left-behind and general populations exposed to the intervention.

13. Participant timeline

This platform trial is embedded within routine screening programmes. From the individual participant perspective, they will flow through the screening programmes as normal; participants will present and have their eyes checked by a first-line screener either in their own home, at a school, local clinic, or community meeting place, depending on the setting. The screener will ask a series of sociodemographic questions and perform a 'tumbling E' visual acuity assessment, all using the Peek smartphone app. Those who screen positive will be referred to a local triage centre where their eyes will be re-checked by a more highly skilled practitioner and treatment will be delivered. Those requiring more advanced care will be referred on to the appropriate service provider.

Some programmes use a roaming team of screeners who visit communities sequentially. Others train screeners who remain in one location. Table 2 summarises the two approaches.

Table 2: Different screening programme approaches

	Outreach screening model	Primary care screening model
1. Community-based screening	Outreach screeners trained to use the Peek app attend schools/local venues and screen those who are present before moving to the next location	Primary care staff are trained to use the Peek app to opportunistically screen and refer those who present to primary care
2. Referral to triage	Those who screen negative (i.e. with no eye health need) are discharged. Those who screen positive provide their contact details and answer a series of socioeconomic questions. They are then referred to triage.	
3. Triage, basic treatment, & further referral	An ophthalmic nurse checks-in attenders using the Peek app and then performs an eye examination. Simple treatments are provided for basic issues (e.g. eye drops for conjunctivitis). Other cases are referred for refraction and/or further care. Referral status is recorded in the Peek app.	
4. Specialist treatment	A receptionist checks-in those who present to receive refraction or further ophthalmic treatment using the Peek app at the secondary or tertiary clinic.	

In some settings, triage will be co-located with screening. In others it will be co-located with the provision of refractive services, and in others it will be co-located with refraction and all other specialist treatment providers i.e. in a hospital. Figure 3 shows the three different configurations of screening, triage, and treatment.

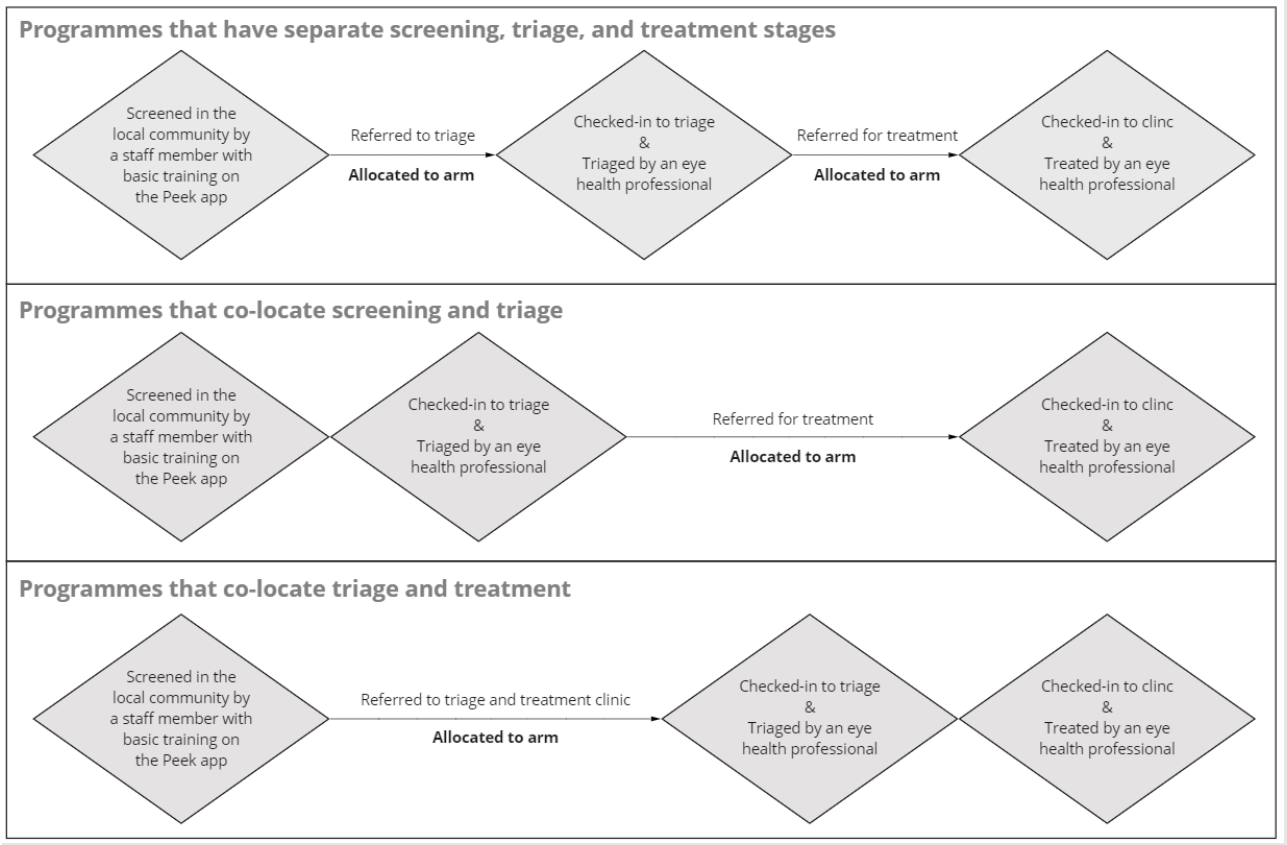

Figure 3: Flow through a generic screening programme for those requiring treatment

Most programmes aim to progress to a model of co-locating triage with screening or treatment in order to reduce the appointment burden on participants and minimise loss-to-follow-up. In the former case, participants testing positive at screening are 'referred' to a room next door for triage. In the latter case, they are given an appointment to attend a central triage & treatment clinic, commonly 1-2 weeks after screening. In most programmes SMS reminders are sent on the date of referral and the day before the appointment. Interventions will be allocated by the algorithm at the point of referral.

14. Sample size

As we are using stopping rules, will not pre-specify a minimum sample size or estimate effect sizes for the intervention arms. Instead, participants will be continually recruited until we reach a pre-determined maximum sample size or sufficient data accrue to trigger one or more of the other stopping rules. Triallists have argued that this approach is more "efficient, informative and ethical" than traditional fixed-design trials as this approach optimises the use of resources and can minimise the number of participants allocated to ineffective or less effective arms.[22] Every 72 hours the algorithm will review the attendance data and calculate the probability of attendance within each arm.

Operating characteristics for individual trials of interventions administered to individual participants

Based on extensive scenario modelling, we have decided to use the following stopping rules for individual trials that test interventions administered to individuals (rather than clusters):

1. There is a >x% probability that one arm is best. (Default x = 95%)
2. There is a >y% probability that the difference between the arms remaining in the trial is <1%. (Default y = 95%)
3. Maximum sample size = n. (Default n = 10,000).

The overall platform trial will be stopped once attendance reaches or exceeds 80% for every sociodemographic group in a given site.

We conducted simulations to estimate the impact of the early stopping rules on error rates and sample sizes. For both rules, 95% threshold values were used as default. We assumed a fixed 1:1 ratio for two-arm trials where the control arm had 50% outcome rate and the intervention arm has an effect difference of d, ranging from 0% to 5%. A total of 1,000 simulations were conducted for each value of d, and we assumed that interim analysis would take place for every 100 outcomes observed.

Table 3. Expected error rates and sample size, by true effect difference between arms (d)

True effect difference between arms (d)	Type I error (α)	Type II error (β)	Median sample size [IQR]
0%	32.1%		19,950 [3075,43525]
1%		8.4%	8,150 [2500,22650]
2%		3.1%	3,800 [1500,8100]
3%		1.8%	2,100 [1000,4100]
4%		0.4%	1,600 [900,2700]
5%		0.6%	1,200 [700,2000]
10%		0%	500 [400,800]
15%		0%	300 [300,400]
20%		0%	200 [200,300]
25%		0%	200 [200,200]

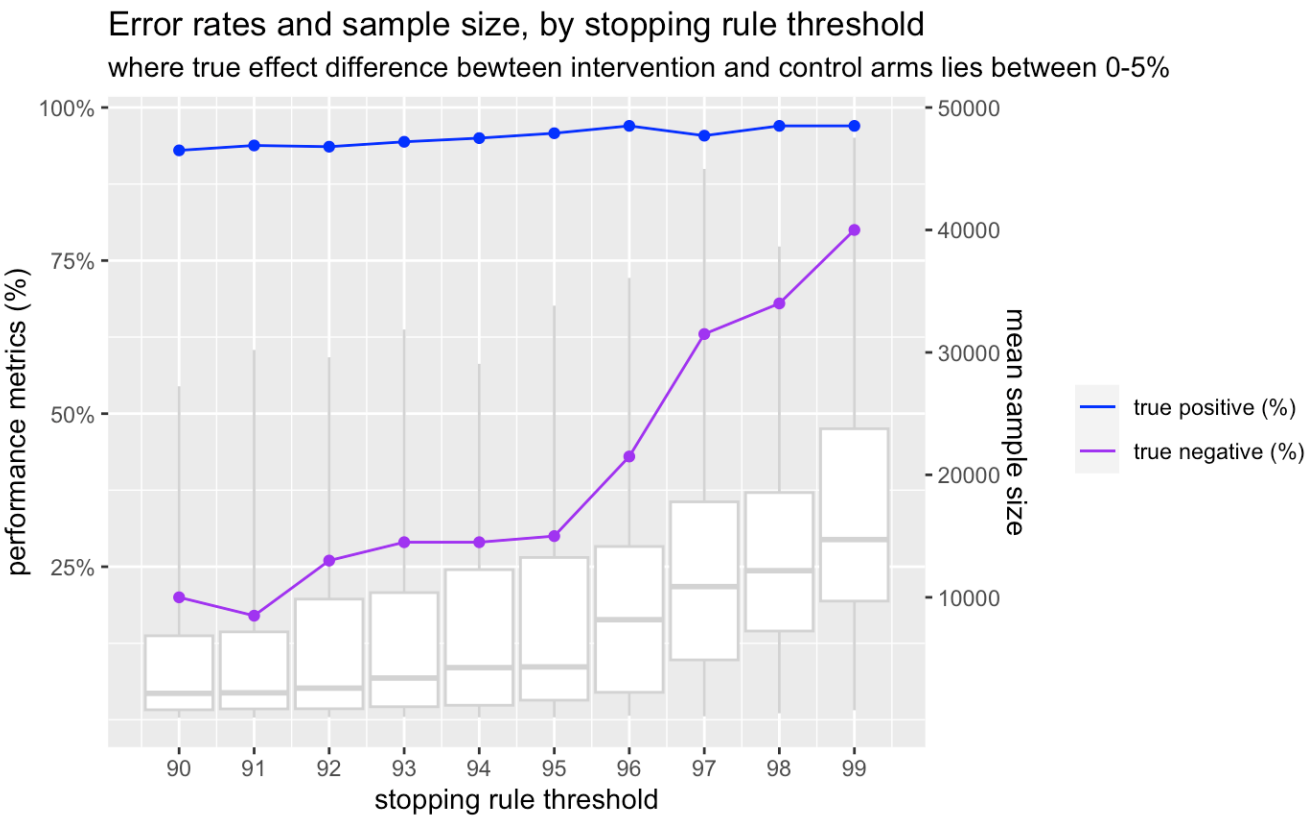

Figure 4. Expected error rates and sample size, by changing stopping rule threshold

In this trial, we prioritize high statistical power (1- β). Minimizing β will protect against the risk of incorrectly identifying an inferior arm as a winning arm. Simulation results show that the expected power in our trial will be at least 98% when an intervention arm is more effective than the control arm by a difference of 3% or greater. When the winning arm is only marginally more effective by a difference of 1%, our trial will still ensure a statistical power of 92%, which is greater than the power of 80% used in most conventional trials. It is noted that the high statistical power in our trial comes at the cost of increased chance of committing type I error. Furthermore, it will take longer to run the trial to find smaller differences. When there is no difference between arms, we expect 32% chance of making false positive conclusions (Table 3). But we will treat the risk of committing type I error as not a major concern because we expect no or minimal harm in selecting either of the two arms with equal effectiveness.

The values of posterior probabilities specified in rules 1 and 2 will be determined by our research team at the start of each individual trial. The default values will be 95% as above, however it might be appropriate to use lower thresholds for interventions where the costs and risks are negligible, and higher thresholds when the costs and/or risks are high. For example, to decrease the chance of committing type I errors, the probability threshold in rule 1 will be increased from 95% to a higher value (Figure 4).

Interventions administered to clusters

Where the chosen intervention can only be implemented in clusters rather than randomising individuals to receive the intervention, the local management team will be convened to develop a design tailored to the intervention. An important factor to account for in any design will be determining how much the outcome varies by cluster and how large each cluster is. For cluster-level interventions it is likely we will carry out a more traditional approach with a fixed number of clusters randomised before declaring one arm the winner. The number of clusters randomised will be based on the intra-cluster correlation, the current attendance rate, the size of the clusters and the effect size for which we want to be powered to detect.

15. Recruitment

As the trial is pragmatic, the responsibility for recruiting screening participants lies exclusively with local programme managers. Programme implementers will enrol participants by seeking consent from all those who require referral for further assessment and care.

16. Allocation

16a Sequence generation

We will use computer-generated random numbers to generate the allocation sequence and assign all consented, referred participants to intervention arms, with equal numbers of participants in each arm. Where appropriate blocking will be used with blocks between 4-12. Stratification will be used where appropriate.

16b Allocation concealment mechanism

For interventions delivered to individuals, the allocation sequence will be generated within the Peek system in real-time, as participants are referred. As human trial managers are not involved in allocation there is no need for concealment.

For cluster trials these will be done randomly. Restricted randomisation will likely be used in this scenario to achieve balance between arms.

16c Implementation

The algorithm will be set up so that it can implement digital interventions such as SMS messages without human investigators being exposed to the allocation status of individual participants. For interventions that require human intervention – such as providing transport, chaperones, or physical vouchers, implementers will be informed of individual participants' assignment status via the Peek app at the stage that intervention needs to be delivered.

External independent review of interventions prior to implementation

As and when new interventions are selected for testing, they will need to be externally reviewed by an independent national ethics committee to ensure that the intervention(s) do not pose undue risk. The platform trial is designed to test low/negligible risk service modifications. Coupled with the fact that the master protocol will already have receive ethical approval, this should enable

rapid/expedited ethical review of new interventions rather than full committee review. Table 4 summarises example interventions and risk thresholds.

Table 4: Risk thresholds and example interventions

Level of risk	Descriptor	Example interventions
High	Risk markedly higher than standard care: high probability of physical, psychological, social, or economic harm	N/A
Moderate	Risk somewhat higher than standard care	N/A
Low	Comparable to the risk of standard care	• Vouchers/discounts/subsidies • Changes to which professional perform the screening/triage • Use of different screening technologies e.g new equipment • Use of different medications e.g. eye drops • Free chaperones or transport
Negligible	Small modifications to existing routine programme where the process of obtaining consent would introduce burdens to the patient that are greater than the intervention itself	• Frequency, days, or time of day that reminder SMS messages are sent • Wording of SMS communications • Community sensitisation (e.g. radio commercials/plays/training) • Clinic days, times, and locations • Option to code additional eye conditions (beyond low acuity)Patient flow • Information presented to programme managers e.g. access to a dashboard • Types of reminders e.g. SMS or picture message or voice message or leaflet

17 Masking

17a Who and how

Once assigned by the algorithm, each participant's online record will automatically update to display which arm they have been allocated to. Participants will not be masked to assignment. For interventions that require human delivery (e.g. handing out a paper voucher), implementers will be able to view allocation status out of necessity. Outcome assessment will be performed by a different group - those responsible for checking-in participants at triage clinic. No steps will be taken to mask these staff to participant allocation status. Ongoing interim data analysis will be performed by the Bayesian algorithm every 72 hours.

17b Unmasking

Human investigators and programme managers will not be able to access data on allocation of participants to specific arms unless they are involved in delivering an intervention.

The Data Safety and Monitoring Committee (DSMC) will have access to all data at any point and for any reason, including to unmask assignment if required. The trial steering committee members will only be able to access these data as per the adverse event protocol outlined below.

18 Data Collection

18a Data collection methods

As stated above, outcome assessment (attendance at clinic) will be recorded when participants check-in at clinic on their appointed date. Each participant's attendance status will be recorded on their central record.

18b Retention

There are no plans to promote participant retention and complete follow-up.

19. Data management

All data entry will be performed by programme staff as part of routine screening and clinical care. See the data management plan for further information about coding, security, and storage.

20a Statistical methods

All analysis will be conducted using R. Baseline characteristics of all participants will be described as mean (SD) or median (IQR) for categorical variables, or as frequencies and proportions for continuous variables.

During this adaptive trial, clinic attendance in each arm will be assessed using Bayesian methods. At each prespecified interim analysis point, a binomial distribution of outcome will be described for each arm using the total number of participants allocated to the arm and the number that attended at clinic. The binomial distribution will be combined with a prior distribution to update the posterior distribution of each arm. A regularizing prior of beta(100,100) will be applied to reduce overfitting until a reliable amount of data is accrued. A Monte-Carlo simulation will be used to update posterior distributions at each interim analysis point. Posterior probabilities will be calculated and compared to the stopping rules as to whether the trial should continue into the next day or end early. If there is sufficient evidence to meet one of the stopping rules, the trial will terminate and proceed to the final analysis stage.

Upon completion of the trial, a complete case analysis will be performed on all eligible participants in the trial on an intention-to-treat basis. The primary endpoint of the trial is clinic attendance the left-behind subgroups after randomization. Within a selected subgroup, the primary analysis will use beta-binomial models to estimate the posterior distribution of attendance in each arm. Posterior probabilities will be calculated to compare the proportion of attendance between arms and to identify an arm that results in the highest likelihood of attendance. For the secondary endpoint, beta-binomial models will also be used but expanded to all participants in the trial. A more detailed description of the statistical methods will be reported as open access as a separate statistical analysis plan.

20b Equity analyses

The primary aim of the platform trial is improving equity. We focus on attendance rates in the left-behind group, and also look at how attendance rates in this group compare to those among the entire population.

20c Non-adherence and missing data

Missing data is not a problem because the outcome is attendance. Non-adherence will depend on the intervention. We will use intention-to-treat analysis.

21a Data Monitoring

Data management team

- Nigel Bolster
- Min Kim
- David Macleod
- Luke Allen

Botswana DSMB

- Prof Tsima, Chairperson
- Mr Moremi, Biostatistician
- Ms . Manyothwane, Member, Eye Nurse

Kenya DSMB

- Dr Nyawira Mwangi
- Dr Stephen Gichuhi
- Statistician TBD

Nepal

- Three people have been identified

India

- Dr Shalinder Sabherwal
- Javed Nayab
- Atanu Majmudar (statistician)

In India, data safety and monitoring committee consists of Mr Javed, who will be responsible for overseeing that regular and complete data entry is being made in the designated application daily. The process of syncing of data would be monitored daily by him. Dr Shalinder would be monitoring 10 percent of the data for quality and will monitor that no identifiable data is being shared further for analysis or any other purpose, other than programmatic interventions. Mr Atanu would be monitoring completion of data entry and the trends periodically to provide feedback to the research team.

Composition of data safety and 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

Consent

Written informed consent will be sought by screeners during screening - at the point that participants are identified as having an eye care need and referred on for further care. Consent will be recorded either on paper forms or by using an electronic tick box (as appropriate for low-risk trials). Whichever format is used, consent status will be recorded on the Peek app.

Participants will be given the contact details of the research managers and will be free to leave the trial at any time. There will be no remuneration for participants.

Patient and public involvement

Lay people and community advisory committees have reviewed and contributed to the development of this protocol. The interventions that the platform trial will test will be derived from engagement with affected groups. Lay representatives will assist with interpretation and publication of the trial findings.

22. Adverse event reporting and harms

An adverse event (AE) is defined as any untoward medical occurrence in a patient or study participant. A serious adverse event (SAE) is defined as any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect

Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

All adverse events will be reported. Depending on the nature of the event the reporting procedures below will be followed. Any questions concerning adverse event reporting will be directed to the study coordination centre in the first instance. The flow chart below has been provided to aid the reporting of adverse events.

Non-serious AEs

All non-serious AEs will be reported to the study coordination centre and recorded in a dedicated AE log within 72 hours. The entry must state the patient ID, date and time of AE, nature, and relation to

the intervention, if any. The AE should also be reported to the data and safety monitoring committee within 72 hours. AE logs will be stored on a secure, password-protected file on a LSHTM computer.

Serious AEs

Serious Adverse Events (SAEs) will be reported to the PI and study coordination centre within 24 hours of the local site being made aware of the event (Figure 5). The PI will report the event to the data safety monitoring committee within 48 hours and include it in the study safety report.

An SAE form will be completed and submitted to the PA and study coordination centre with details of the nature of event, date of onset, severity, corrective therapies given, outcome and causality. All SAEs whether expected, suspected or unexpected will be reported to regulatory bodies and the trial DSMB within 48 hours of occurrence. The responsible investigator will assign the causality of the event. All investigators will be informed of all SAEs occurring throughout the study. If awaiting further details, a follow up SAE report should be submitted promptly upon receipt of any outstanding information.

Any events relating to a pre-existing condition or any planned hospitalisations for elective treatment of a pre-existing condition will not need to be reported as SAEs.

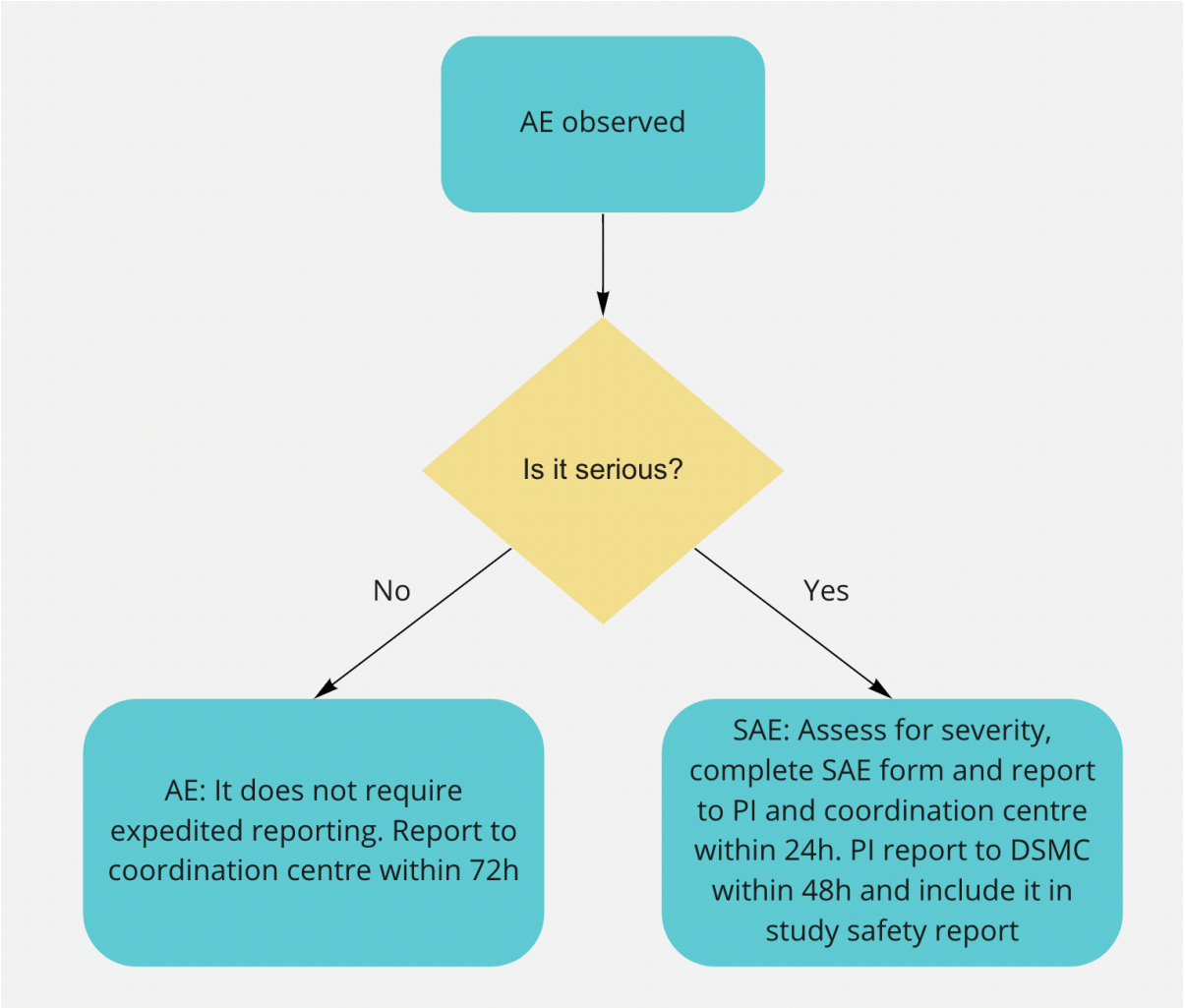

Figure 5: Approach for managing adverse events

Contact details for reporting SAEs

SAE forms will be sent to: luke.allen@lshtm.ac.uk and the relevant in-country co-PI using the title 'Urgent - SAE'

Nepal: smishra@nnjs.org.np
Botswana: nkomazanao@UB.AC.BW
India: shalinder.sabherwal@sceh.net
Kenya: gichangi58@yahoo.com

Tel: +44 (0) 20 7958 8316 (Mon to Fri 09.00 – 17.00, London)

Responsible Personnel

Chief Investigator (CI)

- The CI has overall responsibility for the conduct of the study and the ongoing safety and evaluation of any IMPs being used in the trial.
- Promptly notifying all investigators, Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Competent Authorities (CAs) of each concerned member state of any findings that may affect the health of the trial participants.

- Keeping detailed written reports of all AEs/ARs identified in the protocol as critical to the evaluation of safety within the agreed timeframes specified in the protocol.
- Accurate production and submission of the Development Safety Update Reports and progress reports to CAs and IRB/IECs.
- Collate all AR/AEs/SAEs/SARs and report to the Sponsor annually.
- Ensure that the PIs report all SAEs/SUSARs immediately to the Sponsor and to the CAs, IRB/IECs and any other relevant parties within agreed timelines (
- Supplying the Sponsor and IRB/IEC with any supplementary information they request.

Principal Investigators (PI)

- The PIs have responsibility for the research performed at the local site, handling and management of investigational medical products, and informing the CI, Sponsor, Ethics, regulatory bodies and the trial coordinating team, of all adverse events that occur at their site
- Safety responsibilities:
- Ensure trial participant safety and the swift and adequate management of trial participants with any type of AE/AR as per the management protocol described below.
- Reporting all SAEs/SUSARs immediately to the Sponsor and to the CAs, IRB/IECs and any other relevant parties within agreed timelines (i.e. LSHTM, EFMHACA, ORHB, FMOST).
- Assessing each event for causality, severity and expectedness. (Note: a medical decision which must be made by the investigator directly involved with the care of the patient/participant experiencing the AE)
- Ensure adequate archiving of AE records and reports in the local trial office along with the trial master files.
- Collate all AR/AEs/SAEs/SARs biannually and present to the CI.
- Guide and supervise the field research team on accurate recording, reporting of all adverse events.

Field Research Team Members (Coordinators, Nurses, Examiners, Recorders)

- All field research team members are responsible for identifying, recording, and reporting any AE or AR to the PIs regardless of severity or causality.
- Assessing each event for causality, severity and expectedness. (Note: a medical decision which must be made by the investigator directly involved with the care of the patient/participant experiencing the AE).
- Ensure that the participant has received the necessary management. This includes advice/reassuring, referral, offering transport, paying for management, making follow-up visits
- Report to the PIs/Project manager AEs/ARs based on the specified timeline and file all AE/AR recorded forms in the trial master file.

Frequency and plans for auditing trial conduct

The study may be subject audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, the Study Coordination Centre and other regulatory bodies to ensure adherence to Good Clinical Practice.

Limitations

We have chosen to use a prioritarian approach that focuses on left-behind population groups. This prevents a situation where we accept an intervention that improves the overall mean but is associated with a decline among left-behind groups. This approach does not hedge against the slope of inequality worsening. Unfortunately, using a proportionate approach where we assess whether gains in each group are proportionate to their initial need would risk attributing success to our intervention rather than the more likely detection of regression toward the mean.

Our estimate of the probability/proportion will be biased. Because we choose to stop on average at a "local peak". So for example we're confident A is better than B, but the estimate of the attendance rate in A will be on average an overestimate.

We use attendance as a proxy for access. Whilst this is the closest hard indicator available, the semantic implication of the term places responsibility on people rather than clinical systems or societal structures. We will counterbalance this in the language that we use to talk about barriers and in the framing of interventions. We also note that we focus on a proximal indicator that does not always correlate well with receipt of high-quality care, or good clinical outcomes. We decided to focus on access for three main reasons; first it aligns with the conceptual narrative of Universal Health Coverage and ‘leaving no one behind’, second attendance data are already routinely collected and available for every single person who is referred, and third, internal Peek data suggests that the ‘fall off’ gap between those who are referred but do not attend is much larger than other gaps e.g. the proportion of those who attend but do not receive appropriate care, or the proportion of those who receive appropriate care but do not experience improved health outcomes.

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