The LSHTM Clinical Trials Protocol Template
Version 2.0, September 2021

The SAFER pilot

Semi-automated Allocation For Equitable Research: Automated adaptive allocation and hypothesis testing to increase attendance in a Botswana vision screening programme

The trial will be registered on the ISRCTN registry after it has received ethical and regulatory approval.
https://www.isrctn.com/

SPONSOR: London School of Hygiene & Tropical Medicine

For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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FUNDERS: This work was supported by the Wellcome Trust and NIHR grant number 215633/Z/19/Z.

STUDY COORDINATION CENTRE: London School of Hygiene & Tropical Medicine

LSHTM ethics reference: 26480

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the International Council for Harmonisation Good Clinical Practice (ICH GCP) and/or Medicines for Human Use (Clinical Trials) Regulations 2004 (SI2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, the Sponsor's (and any other relevant) Policies and Standard Operating Procedures (SOPs), and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

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Signature: 	Date:

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Signature:			

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Sponsor

London School of Hygiene & Tropical Medicine is the main research sponsor for this study. For further information regarding the sponsorship conditions, please contact the Research Governance and Integrity Office:

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Funder
This work is funded by the Wellcome Trust and NIHR grant number 215633/Z/19/Z.

This trial will adhere to the principles outlined in the International Conference on Harmonisation Good Clinical Practice (ICH GCP) guidelines, protocol and all applicable local regulations.

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GLOSSARY OF ABBREVIATIONS

DSMC	Data and Safety Monitoring Committee
LSHTM	London School of Hygiene and Tropical Medicine
RCT	Randomised controlled trial
UHC	Universal Health Coverage
WHO	World Health Organisation

KEYWORDS

Adaptive trials
Automated allocation
Automated hypothesis testing
Vision screening
mHealth

STUDY SUMMARY

TITLE Semi-automated Allocation For Equitable Research: automated adaptive allocation and hypothesis testing to increase attendance in a Botswana vision screening programme.

DESIGN Pilot and cost analysis of an algorithm to automatically adaptively allocate participants within an existing vision screening programme, and to perform statistical tests on the ensuing data.

We will pilot the algorithm on a pragmatic parallel four-arm adaptive RCT, testing which wording of SMS reminders is most effective at boosting clinic attendance.

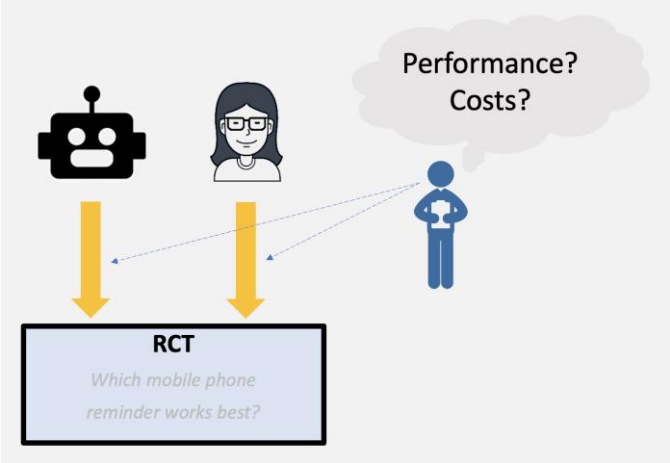
AIMS To test whether an automated allocation and hypothesis testing system can run a small trial to identify the best arm:

1. We want to understand whether the automated system behaves as expected i.e., it adjusts the allocation ratio, drops ineffective arms, and stops the trial when pre-specified conditions are met. We will compare the algorithm's 'decisions' to those made by a human statistician.

2. We want to document the costs involved in setting up and running the system, in comparison with estimated costs for hiring a statistician to perform the same tasks.

3. We are testing the system on a vision screening programme in Botswana. The interventions we have chosen to test are different forms of mobile phone-based reminder messages. The aim is to boost attendance at refractive services.

Figure: Comparing the cost and performance of code vs humans in running a simple RCT



The broader aim of this project is to develop a semi-automated tool that will be used to test interventions intended to improve vision outcomes, with a focus on sociodemographic groups with the lowest attendance rates.

OUTCOME MEASURES

1. Differences in the timing and magnitude of allocation adjustments, dropping of arms, and closure of the trial - comparing algorithm performance against human statisticians who will perform real-time review using the same data and underlying equations and criteria.

2. Direct costs of setting up and running the software, compared to the estimated direct costs of using human statisticians to perform the same work.

3. The primary outcome for the underlying trial is attendance at refractive services on appointed day (yes/no).

POPULATION

Parents/guardians of Batswana schoolchildren aged between 5-18 years who have been identified as requiring refractive services by a school-based vision-screening programme. The programme screens approximately 6,500 children per month.

ELIGIBILITY

Inclusion criteria:

- The nominated parent/guardian of children participating in the Peek Vision school screening programme in Botswana, who test positive at triage and referred on for refractive services on a named day.
- Access to a mobile phone.
- English or Setswana language (>96% of the local population).

INTERVENTIONS The main intervention is the *SAFER algorithm*. Rather than pre-specifying a sample size and comparing mean differences once a prespecified 'n' has been recruited, a response adaptive algorithm will be used that adjusts the allocation ratio based on arm performance. The algorithm can also drop ineffective arms and end the trial once pre-specified thresholds are met.

The comparator to the SAFER algorithm is the performance and estimated costs of human statisticians performing the same tasks i.e. running an adaptive trial.

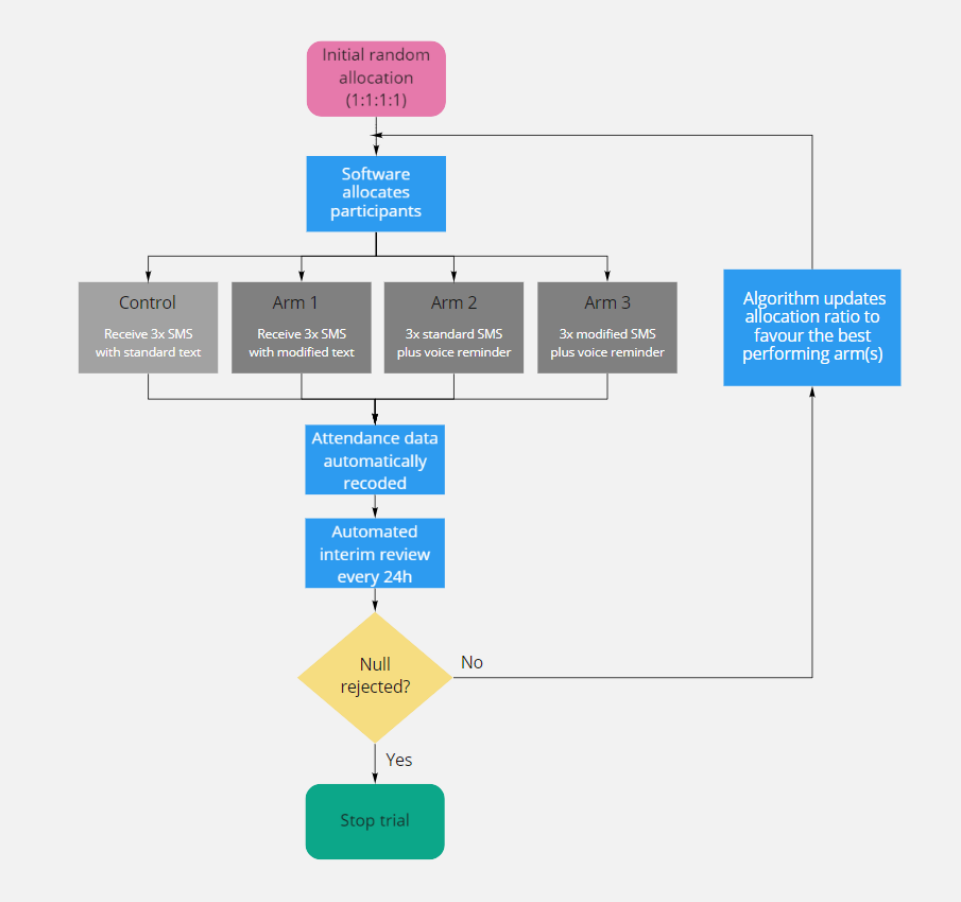
We have deliberately chosen a low-risk intervention for piloting the algorithm; an RCT of four different mobile phone reminder messages prompting attendance at refractive assessment for children who screened positive for vision impairment. Participants will be initially randomised with a 1:1:1:1 ratio, but automated interim analyses will adjust the allocation ratio according to arm performance. The SAFER algorithm will autonomously allocate and send SMS messages, masking programme implementers to allocation status.

- Arm 1- Control: Three reminder SMS messages sent with standard wording.
- Arm 2: Three reminder SMS messages with alternate wording.
- Arm 3: Three standard SMS reminder messages plus a pre-recorded voice reminder.
- Arm 4: Three reminder SMS messages with alternate wording plus a pre-recorded voice reminder.

Note that access to a mobile phone is a pre-condition for entry into the Peek Vision screening programme. Families that do not own their own mobile provide the number of a friend's or a shared device.

DURATION We anticipate that the active trial will run for six months.

Reference diagram for the underlying RCT



1. INTRODUCTION

1.1 BACKGROUND

A safer and more rigorous approach to continuous programme improvement

Many global health programmes experience large mismatches between those identified with a clinical need and those who attend services. Managers and implementers commonly aim to improve their programmes over time in order to close these gaps. This endeavour is encapsulated in the shifting emphasis from *provision* of services and inputs to *achievement* of effective universal health coverage (UHC). The most robust means of evaluating whether programme amendments/ improvements/ adaptations actually confer benefit is by conducting an RCT. However, RCTs are expensive, require specialist statistical support, and can take years to run. As such, most programmes tend to use informal before-after analyses to assess whether programme amendments have made a positive difference. As this approach is open to confounding it is impossible to accurately quantify the contribution made. In addition, the high cost of conducting RCTs exerts a strong pressure to only perform expensive trials for programme amendments that are very likely to be successful. This means that less robust ideas are commonly subjected to lower levels of methodological scrutiny, potentially exposing participants to harmful or useless interventions. Both squander resources and incur opportunity costs.

Ideally, programme managers would be able to run resource-light, real-time RCTs to continuously improve their programmes. The rise of 'A/B testing' in industry sectors such as digital marketing[1] has spawned a wave of low-cost, automated approaches to running real-time pragmatic trials in order to optimise services with high-quality empirical data. As global health programmes increasingly digitise patient flow, opportunities are emerging to build prospective randomisation and statistical testing into administrative software. The adoption of 'built-in' RCT testing would vastly improve the safety of global health programme quality improvement efforts by helping managers to reliably differentiate between effective and ineffective amendments.

Adaptive trials present another means of increasing safety by reducing exposure to ineffective or harmful 'improvements' for interventions where there is a short time-lag between allocation and outcome. Algorithms are increasingly being used to automatically review performance data and continually adjust the allocation ratio to favour the best-performing arm(s), thereby minimising the number of people allocated to ineffective arms. Previous work has demonstrated that the Bayesian 'Thompson' algorithm[2] is a strong contender for this work. It is simple, fully transparent (i.e. not a 'black box'), and identifies dominant interventions just as well as traditional interim analysis.

If found to be effective, our research group aims to deploy the SAFER algorithm as part of a wider programme of work to boost attendance rates and outcome equity within a vision screening programme.

1.2 RATIONALE FOR CURRENT STUDY

Rationale

[1] Fir example see: https://www.optimizely.com/optimization-glossary/ab-testing/

[2] Russo D, Van Roy B. Learning to optimize via posterior sampling. Mathematics of Operations Research. 2014 Nov;39(4):1221-43.

By bringing together low-cost, automated RCT testing and response-adaptive allocation it should be possible to improve the rigour and safety of global health programme modifications in comparison with the status quo. Developing a scalable approach for rapid automated hypothesis testing would help programmes to extend effective universal health coverage and improve their equity impact, supporting the realisation of the Sustainable Development Goals.

Research questions

- Can we use a semi-automated system to adaptively allocate participants to trial arms based on current performance?
- Does the algorithm run as it's supposed to in a real-life programme?
- Does its performance deviate from the decisions made by human statisticians given the same data?
- What unforeseen issues do we encounter when implementing such a system in a large, live programme?
- How much does it cost to set up and run the algorithm, and how does this compare to the standard costs of hiring a statistician to perform the same role?

Note that we use the term 'semi-autonomous' to mean that human oversight is still required to define the interventions, set the model parameters and stopping rules, and monitor safety data.

We have deliberately chosen a very low-risk intervention to test the algorithm, and our secondary research question is around which form of mobile phone reminder message is associated with the highest attendance rate at refractive services.

Hypotheses

- We hypothesise that there will be no significant difference in adjustments to the allocation ratio, the dropping of arms, or the identification of non-inferior arms between the SAFER algorithm and human statisticians performing regular interim review.
- We hypothesise that the initial set up costs for the algorithm will exceed the cost of using human statisticians, however we also hypothesise that the ongoing costs will be low which would defray the costs of future trials.

2. STUDY OBJECTIVES

In this pilot study our primary objective is to test the ability of an algorithm to adaptively allocate participants within an RCT and identify the best arm(s). We want to understand whether the automated system behaves as expected i.e., adjusts the allocation ratio, drops ineffective arms, and stops the trial when pre-specified conditions are met.

We also aim to document the costs involved in setting up and running the system, in comparison with estimated costs for hiring a statistician to perform the same tasks.

Our secondary objective is to identify the most effective of four different SMS reminders in terms of promoting attendance for vision services among those identified with vision impairment within a real-world Batswana screening programme.

3. STUDY DESIGN

Design

Pilot test and economic analysis of the SAFER algorithm, running on a pragmatic, embedded, parallel four-arm adaptive RCT.

Interventions

The algorithm will run a RCT to test four different phone-based reminder messages designed to prompt referred patients to attend for refractive services.

- Arm 1 - Control: 3x reminder SMS messages with standard wording (usual care in the Peek programme)
- Arm 2: 3x reminder SMS messages with alternate wording
- Arm 3: 3x standard SMS reminder messages plus a pre-recorded voice reminder
- Arm 4: 3x *alternate* wording of SMS reminder messages plus a pre-recorded voice reminder

> **Standard SMS reminder message**
> "Dear [name], your child was examined and found to need spectacles. Kindly attend [location] for refraction."
>
> **Alternate SMS reminder message**
> "[Child's name] needs further assessment of their vision to see if reading glasses would help them with their education. They will receive a free assessment on [date] at school between [time-time]. Please ensure that [child] attends on that day. Many thanks, Dr Bastawrous"
>
> **Voice message**
> "Your child was recently assessed by Peek Vision at their school found to have low vision. This may be impacting their schoolwork. Your child has been invited to attend for a reading glasses assessment this coming [day]. Please ensure that they attend their school as usual. If they are found to need glasses, we will provide you with a copy of the prescription, and we can make up a pair of glasses for [xxx] pula. If your child is unable to attend on [day], please press 1 to book an alternate day. Many thanks, the Pono Yame screening team."

To control for any effect the timing of the intervention might have, all SMS will be sent at the same time (6pm).

Duration

Six months

Participants

The participants will be the parents/guardians of Batswana school-aged children (5-18years old) who have been identified as requiring referral on to optometry for refractive assessment, following screening using Peek Acuity testing.

Setting

The trial will run within an existing national school-based vision screening programme in Botswana. The underlying programme will screen approximately 500,000 children in total. The study sites include all government primary and secondary schools nationally (approximately 1,100) across all administrative areas and District Health Management Teams (DHMTs).

Children will be screened and triaged on the same day at their schools. Those identified as requiring refractive services are invited to re-attend on a fixed day within the next three weeks. Adherence has been around 50% in similar school programmes run in other countries. Enrolment will begin in February 2022.

3.1 STUDY OUTCOME MEASURES

1. Differences in the timing and magnitude of allocation adjustments; dropping of arms; and closure of the trial – comparing algorithm performance against human statisticians performing real-time review using the same data and underlying equations and criteria.

2. Direct costs of setting up, running and overseeing the software, and direct costs of using human statisticians to perform the same work.

3. The primary outcome for the underlying trial is attendance at refractive services on appointed day (yes/no).

3.2 RISKS AND BENEFITS

Algorithm

The main risks of automation are delay in the time taken to stop the trial or deviation from the intended mathematical protocol: stemming from bugs in the code, errors in integrating with the screening programme software, or hardware/user issues in the field. These failings could prolong participant exposure to ineffective arms. The potential benefits are the exact reverse; that response adaptive allocation reduces participant exposure to ineffective arms. Automation may also reduce human error. By performing interim analyses every 24 hours (which would be prohibitively expensive for human statisticians), the semi-automated approach may also reach the trial end point faster than the traditional setup, again reducing the number of participants exposed to ineffective arms.

Given that the algorithm we are using performs the same calculations on the same data at the same time as human statisticians, the most likely outcome is that any differences in performance will be negligible.

If the algorithm and testing system is found to operate robustly and at an acceptable cost, then there is a potential wider benefit to society as this approach can be used for a wide range of applications. It also lowers the barriers to performing an RCT in terms of reduced time and costs. Once the algorithm is set up, it can used to test multiple different hypotheses or programme amendments with light-touch human direction. These savings can be used to extend programme reach. We note that statisticians and data safety monitoring will still be required to scrutinise the algorithm's performance, but this is likely to be less time-consuming than performing primary analyses.

Reminder messages

The interventions were selected on the basis that the potential risk to participants is negligible. All SMS reminders will be sent three times. The arms that include a supplemental voice message impose a slightly higher burden on the recipients than usual care.

The potential benefits of the alternate reminder messages are increased chances that children present for refractive services.

The main risk is that the alternately worded SMS and/or voice message will reduce the likelihood that children attend.

We note that the Peek screening programme already has safeguards in place to follow-up non-attenders, so all participants in ineffective arms will be directly contacted and directed to backup services.

Given these backstops, the underlying negligible risk of the interventions (SMS messages), the burden of obtaining informed consent outweighs the burden of the intervention. In line with UK guidance[3] [4] and several similar trials,[5] [6] [7] we do not need to obtain informed consent for this trial as the interventions represent small modifications to existing routine programmes.

4. SELECTION AND WITHDRAWAL OF PARTICIPANTS

4.1 PRE-RANDOMISATION OR PRE-REGISTRATION EVALUATIONS

Participants' children will have their vision screened using the Peek Acuity app as part of a school-based screening programme. Those identified with vision impairment will be triaged that same day. The parents/guardians of all those determined as requiring referral for refractive services at triage assessment will be eligible.

Peek will ensure that all schools being screened have advance warning, so that they can prepare a list of all children, the names of their guardians, and their guardians' contact number. The Peek team will record whether the provided telephone number belongs to the guardian (i.e. they have their own phone), or whether it is for a shared phone.

4.2 INCLUSION CRITERIA

All children participating in the screening programme whose guardians' consent for them to participate.

Inclusion criteria:

- Children aged between 5-18 years participating in the Pono Yame School Eye Health programme.
- Testing positive at screening and determined to have uncorrected refractive error when triaged and referred on for refractive services.

[3] MRC/DH/MHRA Joint Project Risk-adapted Approaches to the Management of Clinical Trials of Investigational Medicinal Products. October 2011. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

[4] HRA and MHRA. Joint statement on seeking and documenting consent using electronic methods (eConsent). September 2018. Available at: https://s3.eu-west-2.amazonaws.com/www.hra.nhs.uk/media/documents/hra-mhra-econsent-statement-sept-18.pdf

[5] Hallsworth M, Berry D, Sanders M, Sallis A, King D, Vlaev I, Darzi A. Stating appointment costs in SMS reminders reduces missed hospital appointments: findings from two randomised controlled trials. PloS one. 2015 Sep 14;10(9):e0137306.

[6] Huf S, Kerrison RS, King D, Chadborn T, Richmond A, Cunningham D, Friedman E, Shukla H, Tseng FM, Judah G, Darzi A. Behavioral economics informed message content in text message reminders to improve cervical screening participation: Two pragmatic randomiz

[7] Berliner Senderey A, Kornitzer T, Lawrence G, Zysman H, Hallak Y, Ariely D, Balicer R. It's how you say it: Systematic A/B testing of digital messaging cut hospital no-show rates. PloS one. 2020 Jun 23;15(6):e0234817.

- Informed consent and agreement to be randomly allocated to one of the four study arms from parents/guardians, and informed assent for children.
- Access to a mobile phone.
- Speaks English or Setswana (>96% of the local population).

4.3 EXCLUSION CRITERIA

- Does not speak English or Setswana
- No access to a mobile phone

5. RANDOMISATION AND ENROLMENT PROCEDURE

5.1 RANDOMISATION OR REGISTRATION PRACTICALITIES

Participants will initially be randomly allocated into four arms using computer-generated blocks of 12. As intervention delivery (sending SMS messages) is fully automated, there is no need for any of the investigators to see participant allocation status. Once the first participants attend refractive services the algorithm will begin adjusting the allocation ratio to favour the best-performing arms. There is no need for the investigators to see allocation status at this stage either. The data safety monitoring committee will be fully unmasked to allocation status and all outcome data and will have the power to stop the trial or suspend any arm.

Threshold for acceptable deviation

We expect some variation between the actual random allocation to each arm per day and the theoretical proportion expected in each arm. If the proportion allocated to an arm deviates by >5% compared to the expected allocation this will trigger deeper investigations as to whether this was by random chance or an actual issue.

5.2 UNBLINDING

Patients cannot be masked. Investigators will remain masked to allocation throughout the study. The algorithm that tests for mean differences does not need to be masked. The only unmasked human investigators will be the data safety monitoring committee. If there are concerns about an arm sufficient to suspend it, participants will be informed. Clinical and programme staff involved in the day to day running of the programme will be informed that one of the arms has been suspended (by email and at staff meetings), however they will not be told which arm.

In the unlikely scenario that there are adverse events or serious adverse events, reporting will go directly to the chief investigator and the data safety monitoring committee, maintaining the blinding of programme implementers, clinicians, and staff involved in the day to day running of the trial.

7. SAFETY REPORTING

7.1 DEFINITIONS

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a patient or study participant
Serious Adverse Event (SAE)	A serious event is 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.

7.2 REPORTING PROCEDURES

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 AEs.

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) (i.e. LSHTM, EFMHACA, ORHB, FMOST, DSMB) 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 (DSURs) 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.

7.2.1 Non-serious AEs

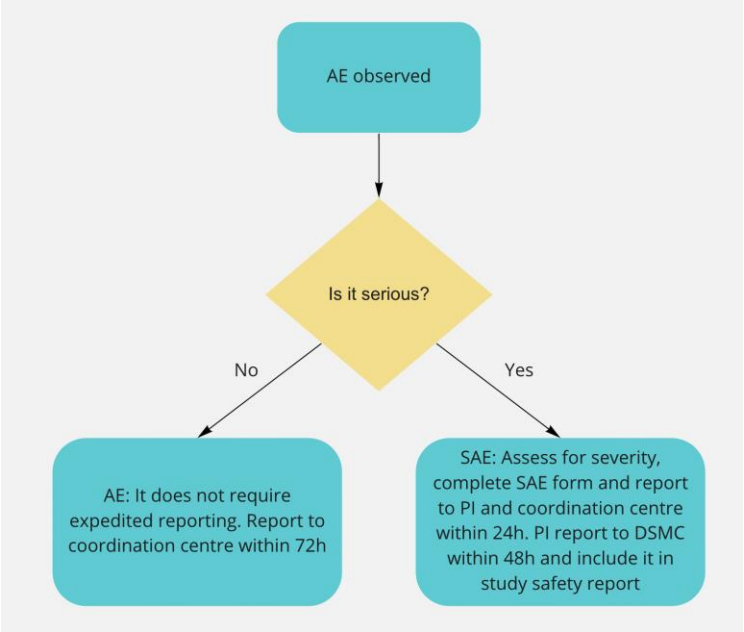
All non-serious AEs will be reported to the study coordination centre and recorded in a dedicated AE log within 72 hours. The entry must state the patient ID, date and time of AE, nature, and relation to the intervention, if any. The AE should also be reported to the data and safety monitoring committee within 72 hours. AE logs will be stored on a secure, password-protected file on a LSHTM computer.

7.2.2 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. 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.



Contact details for reporting SAEs
Please send SAE forms to: luke.allen@lshtm.ac.uk or nkomazanao@UB.AC.BW using the title 'SAE'
Tel: +44 (0) 20 7958 8316 **(Mon to Fri 09.00 – 17.00)**
Tel: [Bots number to be added]

8. ASSESSMENT AND FOLLOW-UP

8.1 RCT primary outcome
All children who are screened and found to need further refractive assessment (e.g. for the fitting of glasses) will be given an appointment, 1-2 weeks later, at a specified time and location. The primary outcome is attendance at this pre-specified appointment (yes/no). The Peek software retains a record of every referred child. When children attend for these appointments they are checked-in using Peek software. This automatically updates their attendance status. The algorithm (and human statisticians) will review this attendance data every 24 hours.

The great advantage of the Peek-based screening programme is that is a closed data system with complete, unified data records for every person screened, their referral status, and their attendance status. No additional data collection activities are required.

8.2 Loss to follow-up
Any participants who do not present for treatment within locally-set timeframes (generally 2-4 weeks from the date of referral) will be followed up by the Peek Vision programme team using their standard protocol, which involves phoning all non-attending patients.

8.3 Trial closure
Once one of the two stopping rules has been satisfied, enrolment will stop and a message will be automatically sent to the PI, lead statistician, and DSMC alerting them to this fact. The programme will revert to sending the control SMS reminder to every participant referred on for refractive services (usual practice).

8.4 Stopping rules
The trial will be stopped when either of the following rules are met:

1. There is a >95% probability that one arm is best.
2. There is a >95% probability that the difference between the arms remaining in the study is <1%.

After formal analysis of the study data, any dominant intervention arm will become the new standard care message sent to every referred participant.

9. STATISTICS AND DATA ANALYSIS

9.1 Sample size
Approximately 6,500 children will be screened every month. Based on previous programmes, we expect approximately 1,000 of these children to be identified as having uncorrected refractive error requiring referral. All of these children's parents/guardians would receive the standard three SMS reminders.

Using a standard analysis, we would perform three comparisons versus the control arm, so would use a Bonferroni adjusted alpha of 0.0167. Assuming 50% attendance on the expected day in the control arm we would need 667 referred children per group to have 90% power to detect an improvement to 60% attendance in the intervention arms (approximately 2700 in total). To detect an improvement to 55% we would require a sample size of 2,692 per group (approximately 10,700 in total). The

disadvantage of the traditional approach to sample size calculations is that the assumptions are often incorrect, leading to over-powering which needlessly exposes participants to ineffective arms, or underpowering which wastes resources.

The adaptive allocation method that we are using does not depend on assumptions, and does not use a pre-specified a sample size. Instead, the study will run until one of two criteria are 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 study is <1%.

This approach is almost perfectly efficient, as exactly the right number of participants are enrolled to answer the research question. Depending on the effect of the interventions, one of the stopping criteria might be met after 100 participants, however it could also take 100,000 before reaching a definitive conclusion. As this is a pilot study to test the practicalities of the algorithm, we propose to set a ceiling on the number of total participants of 3,000.

As we anticipate that 1,000 children will be referred every month, our recruitment should last no longer than approximately three months (but potentially shorter if one of the first two criteria are met).

9.2 Cost assessment

We will capture:

- The costs associated with conception and planning including project development and preparation
- The costs of designing, incorporating/setting up the algorithm, running, and monitoring it
- The counterfactual costs of having human statisticians performing the same analysis

We will collect information on two main costs components: 1) the staff involved and 2) the IT hardware and software equipment used in the trial. We will register a map of interrelations between all the activities performed by all the staff included in the trial (statisticians, epidemiologists, database developer and clinical trial managers) and the resources consumed measured in working hours. By activities we mean, for example, team meetings to conceptualise and plan the trial or algorithm design, and testing and monitoring conducted by the statistician. Staff wages and overheads will be obtained from LSHTM and Peek Payroll services. A list of all IT hardware and software equipment used during the clinical trial will also be recorded including workstation towers, laptops, monitors and printers. IT equipment characteristics, acquisition costs and annual depreciation will be collected from Peek and the International Centre for Eye Health.

All other costs, not directly related to a specific activity, will be included in an overhead cost category estimated at 15% of the cost of all activities performed, including costs connected with infrastructures and the general operation of the organisation, such as depreciation of buildings, water/gas/electricity, maintenances, insurances, supplies and office equipment, communication and connection costs, and costs connected with general services such as administrative and financial management, human resources, training, legal advice, and documentation.

To estimate the costs associated with future amendments/adaptations, a list of all the technical requirements will be produced by the statisticians and epidemiologists. Based on these requirements we will estimate the number of working hours that are needed to adapt the algorithm and therefore estimate the associated costs.

Statistical plan
A CONSORT trial flowchart showing cases assessed, recruited and followed-up by arm will be prepared. Baseline characteristics will be summarised by arm.

At the start of the trial four arms are included and our prior belief is that each of the four arms are equally likely to be the best arm i.e., there is a 25% probability that each arm is the best. As such, at the start of the trial 25% of participants will be randomised to each trial arm. Once outcomes begin to accumulate (typically 1-2 weeks after recruitment) we will update our probabilities that each arm is best based on the accumulated results using a Bayesian framework. We intend to update these probabilities daily, and their results can affect two things.

1. The proportion to be randomised to each arm will change, with more promising arms being given more new enrolled participants and less promising arms receiving fewer (or even none if the probability drops below a certain threshold).
2. The trial can end if one arm is 95% probable to be the best, or there is a 95% probability that the difference between all remaining arms is 1%.

The algorithm will use outcome data to make the reallocations automatically, and to 'decide' whether sufficient evidence has been accumulated to satisfy either of the stopping rules. These calculations will be checked manually (daily at first, with frequency reducing throughout the trial) to ensure that the algorithm's programming works as planned.

Once the study is complete, estimated prevalences and their 95% credible intervals will be presented for each trial arm. Frequentist analysis will be performed on the data as well for comparison.

Assessment of compliance

The mobile software that sends messages will record if each message has been received. We will supplement our intention-to-treat analysis with a sub-analysis that excludes participants who did not receive or open the reminder messages.

Data and all appropriate documentation will be stored for a minimum of 5 years after the completion of the study, including the follow-up period.

According to the data agreement Peek has with the government, Peek will delete personal data from their servers every 9-12 months, with agreement from the MoHW. Anonymised data will be retained for further reporting, sharing and design purposes.

8 MONITORING

A. RISK ASSESSMENT

This study has been designed to test the performance of automated software. As such, we have deliberately selected very low-risk interventions that represent minor modifications to the existing

routine programme. The trial coordination committee will discuss the wording of the SMS messages and the voice message with local Batswana programme implementers and the Peek Batswana Technical Working Group to ensure that the language is appropriate and unlikely to cause distress.

B. MONITORING AT STUDY COORDINATION CENTRE

Monitoring at the Trial Coordination Centre
The trial coordination centre statisticians will check the study date every day that the trial runs for. They will interrogate the allocation 'decisions' made by the algorithm with reference to the underlying equations. The coordination centre will also be responsible for checking consent forms and reviewing and investigating missing or unusual data values.

Monitoring by the Data and Safety Monitoring Board (DSMB)
An independent Data and Safety Monitoring Board (DSMB) will be appointed by the trial steering committee. The DSMB will have three members, all independent of the running of the trial with relevant clinical and epidemiological experience.

The DSMB will confirm their specific meeting arrangements. It is proposed that the DSMB would meet prior to the beginning of the trial (January 2022), one third of the way through, and at the end, to assess the safety of the trial procedures. The DSMB will agree the way it will monitor the data, what it requires from the investigators in this respect and will communicate this to the PIs. All data can be interrogated remotely in real-time.

The DSMB may visit the study coordination centre to assess data management, record keeping and other important activities. The DSMB will determine the manner in which it will monitor the data, what it requires from the investigators in this respect and will communicate this to the PIs.

C. MONITORING AT LOCAL SITE

The trial coordination centre will monitor adverse events passively in all communities through a key informant system; instructing programme implementers and school heads to report any adverse events up to three months after the last reminder message has been sent to a child from the respective school. This approach is proportional to the level of risk posed by the interventions.

The remote team will liaise closely with the programme manager based in Botswana who will also have full access to the data. Due to the pandemic, it is not clear how many site visits will be possible, but we intend to have our PI Luke Allen visit the local sites at least once during the trial – as long as the LSHTM travel guidance allows, and will full COVID-19 safety measures in place.

For severe adverse events our key informants will ensure that individuals are referred to the nearest health facility for appropriate care – if appropriate - and contact the study team.
The DSMB may visit the field work in the community to the conduct of this, assess data management, record keeping and other important activities. The DSMB will determine the way it will monitor the field work elements and will communicate this to the PIs. The DSMB will monitor recruitment and implementation of procedures as per standard protocols and will visit recruitment sites.

The study also may be subject to audit by the London School of Hygiene & Tropical Medicine under their remit as sponsor, and by other regulatory bodies to ensure adherence to GCP. Both active and

passive monitoring systems for adverse events are in place for this study, and these monitoring activities will specifically include (but will not be limited to) treated children of five years and under.

9 REGULATORY ISSUES

11.2 ETHICS APPROVAL

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 and later revisions. The study will comply fully with the Botswana Data Protection Act of 2018.

The Study Coordination Centre will obtain approval from the LSHTM Research Ethics Committee, as well as the University of Botswana Research Ethics Board (Office of Research and Development). The study will only begin in the country after approval certificates have been received from each of the country specific review bodies.

Regular progress reports will be produced throughout the course of the study and shared with the ethics and other review bodies. A trial terminal report will be submitted to the organisations listed above.

Important protocol modifications (e.g., changes to eligibility criteria, outcomes, analyses) will be emailed to relevant parties (e.g. investigators, programme implementers, REC/IRBs, trial participants, and trial registries where appropriate).

11.3 CONSENT

The SMS interventions represent minor modifications to existing routine processes and present negligible risk to participants. Obtaining consent would introduce burdens to the participant that are greater than the intervention itself. As such, we will not seek informed consent.

11.4 CONFIDENTIALITY

Any participants' identifiable data collected by the Study Coordination Centre will be stored in a secure Peek Vision database. Confidentiality protected in accordance with the Data Protection Act 2018. Identifiable patient-level data will not be shared with any other organisation. All published findings will be at anonymous aggregate subpopulation level.

Data storage

Patient personal identifiers will not be stored separately from clinical and other sensitive data in the Peek server. All aggregated data sent to LSHTM-based research staff for statistical analyses will have names removed.

11.5 INDEMNITY

London School of Hygiene & Tropical Medicine holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial.

11.6 SPONSOR

London School of Hygiene & Tropical Medicine will act as the main sponsor for this study. Delegated responsibilities will be assigned locally.

11.7 FUNDING

This work is supported by the Wellcome Trust and NIHR grant number 215633/Z/19/Z.

11.8 AUDITS AND INSPECTIONS

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 GCP.

11.9 PROTOCOL DEVELOPMENT

This protocol was developed by the following investigators who are responsible for the development of, and agreeing to, the final protocol. Subsequent changes to the final protocol will require the agreement of the TSC.

Dr Luke Allen, luke.allen@lshtm.ac.uk

Prof Oathokwa Nkomazana, nkomazanao@ub.ac.bw

Dr Michael Gichangi, gichangi58@yahoo.com

Prof Andrew Bastawrous, andrew.bastawrous@lshtm.ac.uk

Prof Matthew Burton, matthew.burton@lshtm.ac.uk

Dr David Macleod, david.macleod@lshtm.ac.uk

Min Kim, min.kim@lshtm.ac.uk

Dr Nigel Bolster, shnb12@lshtm.ac.uk

Dr Ari Ho-Foster, hofostera@ub.ac.bw

12. TRIAL MANAGEMENT

A Trial Management Group (TMG) will be appointed and will be responsible for overseeing the progress of the trial. The day-to-day management of the trial will be co-ordinated through the LSHTM Study Coordination Centre.

TMG members:

Dr Luke Allen PI
Prof Oathokwa Nkomazana PI
DrMichael Gichangi
Prof Matthew Burton
Dr Nigel Bolster
Dr David Macleod
Ms Min Kim

Dr Jacqui Ramke

Dr Andrew Bastawrous CI

A Data Safety Monitoring Committee will be convened to scrutinise the algorithm's performance.

13. PUBLICATION POLICY

Scientific results will be published in Open Access in peer-reviewed journals and presented at relevant international conferences. All publications and presentations relating to the study will be authorised by the Trial Management Group. The first publication of the trial results will be in the name of the Trial Management Group members. Members of the Data Monitoring Committee will be listed and contributors will be cited by name if published in a journal where this does not conflict with the journal's policy. Authorship of any parallel studies initiated outside of the Trial Management Group will be according to the individuals involved in the project but must acknowledge the contribution of the Trial Management Group and the Study Coordination Centre.