Statistical Analysis Plan

PROSPER II (PROductivity Study of Presbyopia Elimination among aRtisans: a randomised trial on the effect of providing near glasses on the productivity of Indian textile workers)

DOCUMENT HISTORY

Version	Date	Edited by	Comments	Timing in relation to unblinding
1.0	TBD	GM	Approved by signatories, updated to version 1.0	Prior to trial registration

CONTRIBUTORS

Nathan Congdon (QUB), Anant Nyshadam (UMICH), Ling Jin (ZOC), Smit Gade (GBL), Graeme MacKenzie (Clearly Initiatives)

1. TABLE OF CONTENTS

2. INTRODUCTION

This document details the proposed presentation and analyses for the main analysis reporting results from the USAID and Clearly funded randomised controlled trial PROSPER II (PROductivity Study of Presbyopia Elimination among aRtisans: a randomised trial on the effect of providing near glasses on the productivity of Indian textile workers). The results reported in this publication will follow the strategy set out here. Subsequent analyses of a more exploratory nature will not be bound by this strategy, although they are expected to follow the broad principles described. The principles are not intended to curtail exploratory analysis (for example, to decide cut- points for categorisation of continuous variables), nor to prohibit accepted practices (for example, data transformation prior to analysis), but they are intended to establish the rules that will be followed, as closely as possible, when analysing and reporting the trial.

The analysis plan will be available on request when the principal manuscripts are submitted for publication. Suggestions for subsequent analyses by journal editors or referees will be considered carefully and carried out, as far as possible, in line with the principles of this analysis plan.

Any deviations from the statistical analysis plan will be described and the rationale given in the final report of the trial. The analysis will be carried out by an identified, appropriately qualified and experienced statistician, who will ensure the integrity of the data during processing. Examples of such procedures include quality control and evaluation procedures.

3. PERSONNEL

Chief Investigator

Professor Nathan Congdon, Queen's University Belfast, UK

Principal Investigators

Professor Achyuta Adhvaryu, University of Michigan, USA

Professor Anant Nyshadam, University of Michigan, USA

Professor Nathan Congdon, Queen's University Belfast, UK

Trial Statisticians

Ling Jin, Zhongshan Ophthalmic Center, PRC

4. BACKGROUND INFORMATION

4.1 Rationale

PROSPER II is a randomised controlled trial (RCT) assessing the effect of reading glasses on the productivity of presbyopic textile workers in Bangalore, India.

4.2 Objectives of the trial

Globally, 2.7 billion people do not have the eyeglasses they need to earn, learn, travel safely in traffic and participate in civic life. Among these, 1.1 billion people lack a simple pair of reading glasses to correct impaired near vision, called presbyopia.[1] Presbyopia, the essentially universal decline in unaided near vision that occurs with aging, is the world's most common cause of vision impairment. Loss of accommodation (ability to change focus from distance to near) due to presbyopia can begin as early as age 30 years, commonly becomes functionally apparent by 40, and is essentially complete by 55, meaning that presbyopia is most common at the height of the working years. Few trials have been published which address the question of whether healthcare interventions can improve work performance as well as workplace retention, especially among persons over the age of 40 in low and middle-income countries (LMICs).[2-4] We propose to carry out a randomized trial measuring the effect of presbyopic correction on productivity in Indian textile workers in the Bangalore area.

PROSPER II will assess the impact of free reading glasses on productivity for workers in textile factories in Bangalore, India. We hypothesise that the change in worker efficiency over the 3-month evaluation period will be greater in the Intervention compared to the Control group, adjusting for baseline efficiency.

4.3 Trial design

PROSPER II is an investigator-masked, multi-center randomized controlled trial.

4.4 Eligibility

4.4.1 Inclusion criteria

Shahi employees will be eligible to participate if:

- they are aged 30 years or older
- have an unaided distance visual acuity of 6/12 or better in both eyes
- have presbyopia, defined as the inability—correctable with reading glasses—to read the N8 line using both eyes together, on a tumbling E near vision chart at 40cm
- have worked in the sewing department for 3 months or more

4.4.2 Exclusion criteria

Shahi employees will be ineligible to participate if:

- they own reading or distance glasses (regardless of accuracy)
- have ocular pathology in either eye detected during the eye examination, or history of such disease based on self-report
- have a low likelihood of completing follow-up in the study due to current plans to move out of the area or leave employment at Shahi during the follow-up period

4.5 Interventions

Eligible participants will be randomly assigned to Intervention and Control Groups (1:1). Intervention group participants will receive free reading glasses within a week of

undergoing a vision screening at the factory. Control group participants will receive reading glasses at the end of the assessment period (three months after vision screening). The trial will be investigator-masked, but not participant-masked, because the investigators do not feel provision of zero-power glasses to the control group is ethical. However, participants will have limited knowledge of the study hypothesis, limiting potential placebo effects.

4.6 Definition of primary and secondary outcomes

4.6.1 Primary outcome

The primary outcome for sew-ers enrolled in the study is efficiency, defined as the number of items completed divided by target number of items per unit time (as defined by industry standards). Daily mean efficiency for each participant will be assessed from trial entry to closure as recorded in Shahi's Manufacturing Execution System software (SIPMONlite).

4.6.2 Secondary outcomes

The secondary outcomes are:

- changes in skill grade and associated change in wage
- adherence with spectacle wear
- worker self-reported self-efficacy
- Quality of Life using the THRIVE Near Vision Quality of Life tool.
- intervention cost-benefit analysis

4.7 Hypothesis framework

PROPSER II is a superiority trial comparing glasses wear to non-wear. Analysis of the trial will entail calculation of treatment effect measures and confidence intervals to assess the difference between the two arms. Results from the statistical analysis will generally be presented by two-sided confidence intervals (CIs) with a confidence level of 95%. Superiority will be claimed if the two-sided p-value is less than 5% and the treatment estimate favours the use of glasses. If the lower limit is above 0, superiority of glasses-wear against non-wear can be concluded.

4.8 Sample size & power

The primary outcome is efficiency, defined as the number of items completed divided by target number of items per unit time as defined by industry standards. Efficiency is thus a dimensionless ratio. We will top code the efficiency at 99th percentile to account for outliers. This outcome will be compared between the two study groups. An increase in mean efficiency of 0.0425 in the intervention group compared to the control group (the latter having a baseline mean of 0.53 per day and SD 0.19, based on Shahi records) is deemed economically meaningful to Shahi. Effects of this size have been detectable in other trials in this setting. With a two-sided significance level of p=0.05, power of 90% and a serial correlation in outcomes of 0.8 (data from previous Shahi trials), our sample size calculation yields a required sample size of 152 subjects per group.[5] Allowing for 80% adherence and 10% loss to follow-up each month, we calculated that a sample size of 500 individuals (250 per group) is required.

4.9 Intervention allocation

Consenting participants eligible for the trial will be divided into eight strata according to age (<median, ≥median), work tenure at the textile factory (<median, ≥median), efficiency during baseline assessment (<median, ≥median). Participants in each stratum will be randomized 1:1 with block size of four to either the Intervention or Control Groups. The randomisation sequence will be generated by the study statistician at the Clinical Trials Unit of the Zhongshan Ophthalmic Center (Guangzhou, China) using an online random number generator (www.randomization.com), and concealed until a worker is determined eligible and has agreed to participate. The field team will have a list provided by the textile factories of potential participants, their current age, tenure and baseline productivity. Study personnel will access the random assignment for each participant according to the correct age-tenure-productivity stratum only at the time of enrolment.

4.10 Data collection schedule

4.10.1 Data collection before trial

Demographic data will be collected through Shahi's Human Resource database and clinical information will be collected using VisionSpring's Eye Examination Form (Annexe 1). Baseline efficiency data for enrolled workers will be collected from Shahi for an 8-week baseline period prior to randomization.

4.10.2 Data collection during trial

Daily efficiency data for each employee in the sewing department are collected routinely by Shahi on their Manufacturing Execution System software (SIPMONlite). Wage and employment status data will be collected on a monthly basis from Shahi's Human Resource division. These data will be assessed at the end of the 3-month intervention period. Intervention costs will be collected by VisionSpring and assessed at the end of the 3-month intervention period. Secondary outcome data will be collected using the following data collection forms

- Baseline Assessment (following eye examination)
- Endline Assessment (at the end of the 3-month intervention period)
- Spectacle Wear Compliance (on a weekly basis over the 3-month intervention period)

4.11 Interim analyses and stopping rules

Given the low risk to subjects and the relatively short duration of the trial no interim analyses will be conducted. An independent Data Monitoring Committee (DMC) will not be established for PROSPER II.

4.12 Trial reporting

The trial will be reported according to the principles of the CONSORT statement.

5. PROTOCOL DEVIATIONS

A protocol deviation is defined as a failure to adhere to the protocol such as the wrong intervention being administered, incorrect data being collected and documented, errors in applying inclusion/exclusion criteria or missed follow-up visits due to error.

5.1 Major

The following will be defined as major protocol deviations:

- Enrolled workers have not provided Informed Consent
- Data considered fraudulent

5.2 Minor

The following will be defined as minor protocol deviations:

5.2.1 Participants randomised in error

- Employees < 30 years, or employed < 3 months, or not employed in the sewing department assigned to Intervention Group

5.2.2 Participants who do not receive allocated intervention

- Workers in the Intervention Group not receiving glasses
- Workers in the Control Group received glasses from VisionSpring (workers in the Control Group deciding to purchase glasses from an external eyecare service provider during the course of the study will not be considered a protocol deviation, and their data will be analysed under Intention To Treat)

6. ADHERENCE TO THE INTERVENTION

Adherence to the intervention will be assessed through observation of spectacle wear while working. Adherence will be measured surreptitiously on a weekly basis. The enumerators assessing spectacle wear compliance are GBL staff members familiar to Shahi workers.

7. ANALYSIS POPULATIONS

7.1 Primary analysis strategy

All outcomes will be assessed by Intention To Treat: participants will be analysed in the groups into which they were randomly allocated, i.e. comparing the outcomes of all workers allocated to the Intervention Group with workers allocated to the Control Group, regardless of allocation received.

7.2 Descriptive analysis population

Baseline demographic and clinical characteristics will be reported for all workers randomised for whom we have data available, excluding protocol deviations randomised in error where Informed Consent has not been obtained.

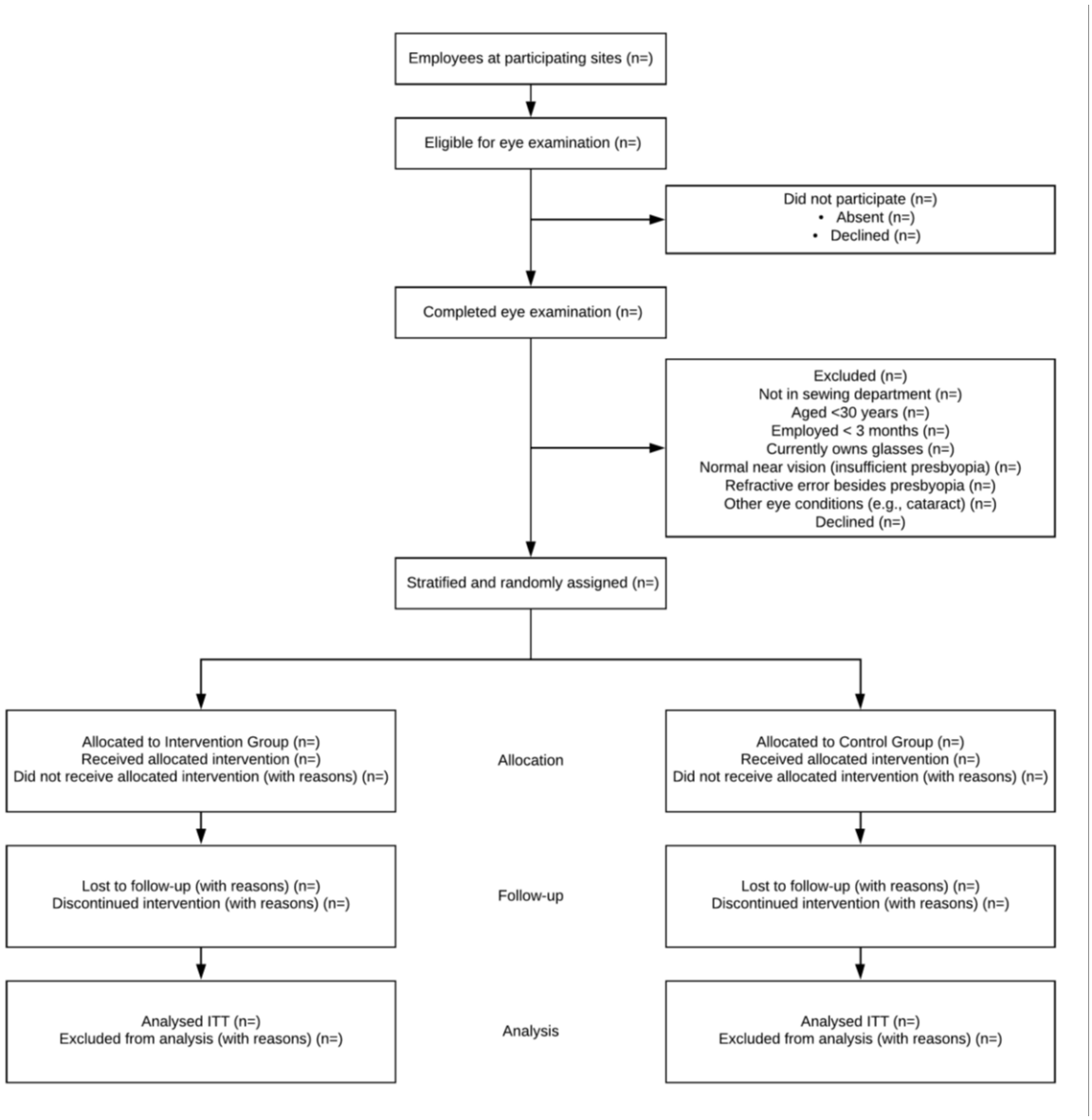
8. DESCRIPTIVE ANALYSES

8.1 Representativeness of trial population and participant throughput

The flow of participants through each stage of the trial will be summarised using a CONSORT diagram (see below). We will report the numbers of participants:

- at participating sites
- eligible for eye examination
- examined
- stratified and randomly assigned
- received intended intervention
- withdrawals
- randomised in error
- included in the analysis

CONSORT Flow Diagram



8.2 Baseline comparability of randomised groups

Participants in randomised groups will be described separately with respect to the following characteristics at trial entry:

- age
- sex
- education level
- marital status
- number of children and dependants
- median wage compared to urban Bangalore and urban India
- near vision quality of life (THRIVE tool)
- uncorrected visual acuity in each eye separately at distance and both eyes together at near
- mean power of near correction required
- baseline work productivity
- worker self-efficacy
- attitudes towards vision correction
- access to local eyecare services
- history of uptake of eyecare services

Numbers (with percentages) for binary and categorical variables and means (and standard deviations), or medians (with lower and upper quartiles) for continuous variables will be presented; there will be no tests of statistical significance performed nor confidence intervals calculated for differences between randomised groups on any baseline variable.

8.3 Losses to follow-up

Missing data due to loss to follow-up is likely to be linked to staff turnover. Worker turnover at Shahi is accounted for in the sample size calculation and, based on historical data, is not expected to exceed 10% per month.

8.4 Adherence to intervention

The percentage of glasses wear adherence per week will be reported for the duration of the trial.

9. COMPARATIVE ANALYSES

9.1 Analysis of primary and secondary outcomes

The primary endpoint is difference in efficiency during the 3 months of intervention between the treatment and control groups. The objective is to show that glasses-wear is superior to non-wear in improving worker efficiency. The null-hypothesis will be rejected on a 5% level if the two-sided 95% CI of the treatment full analysis set difference $\mu_{glasses} - \mu_{non\text{-}glasses}$ excludes 0. If the lower limit is above 0, superiority of glasses wear against non-wear can be concluded. The hypothesis will be tested using an analysis of covariance (ANCOVA) model. In the regression specification, the outcome variable will be daily mean efficiency

for each participant per day. The factors, covariates and interaction terms in the ANCOVA model are listed in the table below.

Factors and covariates at baseline	Type	Categories
Randomised treatment	Factors	Intervention, Control
Sex	Factors	Male, Female
Skill grade	Factors	<median, ≥median
Factory type	Factors	Urban, rural
Spectacle wear compliance	Factors	<median, ≥median
Self-reported self-efficacy	Factors	<median, ≥median
Age	Covariate	Not applicable
Baseline efficiency	Covariate	Not applicable

The factors and covariates will be included in the model as main effects in an additive structure. The estimated treatment difference between glasses-wear and non-wear will be reported together with the associated two-sided 95% CI and corresponding p-value. The standard errors will be clustered at the individual participant level.

Linear regression analyses will be performed on potential determinants of primary and secondary outcomes. The study group and all significant variables with p values less than 0·20 in simple regression analyses will be included in multiple regression models. Histograms, normal quantile plots (QQ Plot), and the Shapiro-Wilk normality test will be used to test the normality assumption in regression models. For the Visual Quality of Life (THRIVE) tool, a composite score (eleven items) and near activities sub-score (five items) will be created on 0–100 scales. Intervention costs will comprise the screening test, glasses (and any replacement thereof) as well as direct and indirect costs to the company for facilitating workplace-based sight tests. We will report cost effectiveness distinguishing between study costs and program costs. The cost effectiveness analysis will include both the costs to identify presbyopia and treat presbyopia.

The analysis of primary and secondary outcomes will be adjusted for the minimisation factors (age, work tenure at the textile factory, efficiency during baseline assessment) to account for the correlation between treatment groups introduced by balancing the randomisation.[6] Both the crude unadjusted and adjusted estimates will be presented, but the primary inference will be based on the adjusted analysis.

For multiple imputation of missing data in assessing primary outcomes we will create 20 copies of the data, in which missing values shall be imputed by chained equations, and the datasets will be averaged.

9.2 Pre-specified subgroup analysis

The consistency of the effect of the intervention across specific subgroups will be assessed using the statistical test of interaction. Pre-specified subgroup analyses include:

- Sex
- Skill grade (<median, ≥median)

- Reading glass power (low, reading glasses powers < 1.25D; moderate,1.25D <= reading glasses powers < 2.00D; high, reading glasses powers >=2.00D)
- Age group (30 to 40years, 40 to 50 years, 50 years and older)

Subgroup analysis will be performed on the primary outcome.

9.3 Significance levels and adjustment of p-values for multiplicity

For the primary outcome, including subgroup analyses, a 95% confidence interval will be calculated. 99% confidence intervals will be used for the secondary outcomes, to take account of the number of comparisons.

9.4 Procedure for accounting for missing, unused, and spurious data

Missing data will be described, for example, by presenting the number and percentage of individuals in the missing category. All data collected on data collection forms will be used, since only essential data items will be collected.

9.5 Exclusion of data

Before data are locked for statistical analysis, a blinded review of all data will take place. Any decision to exclude a subject or single observation from the statistical analysis is the joint responsibility of the PROSPER II trial statistician, the international trial manager and the Chief Investigator. Exclusion of data from analyses will be used restrictively and normally no data should be excluded from the full analysis set. The subjects or observations to be excluded, and the reasons for their exclusion will be documented and signed by those responsible before database lock. The subjects and observations excluded from analysis sets, and the reason for this, will be described in the clinical trial report. Any observation excluded from the analysis database will be documented before database lock with the reason for exclusion provided.

9.6 Statistical software employed

Stata, version 16.1

10. SAFETY DATA ANALYSIS

10.1 Serious adverse events

Serious adverse events will be listed by allocation as well as allocation received.

11. ADDITIONAL EXPLORATORY ANALYSIS

Any analyses not specified in the analysis protocol will be exploratory in nature and a 2-sided significance level of 0.01 will be used with 99% confidence intervals.

12. DEVIATION FROM ANALYSIS DESCRIBED IN PROTOCOL

None at present

13. REFERENCES

1. Fricke TR, Tahhan N, Resnikoff S, et al. (2018) Global Prevalence of Presbyopia and Vision Impairment from Uncorrected Presbyopia. Ophthalmology;125(10): 1492—1499.
2. Li R, Chen X, Yan H, Deurenberg P, Garby L, Hautvast JGAJ. Functional consequences of iron supplementation in iron-deficient female cotton mill workers in Beijing, China. Am J Clin Nutr 1994; 59: 908—913.
3. Wolgemuth JC, Latham MC, Hall A, Chesker A, Crompton DWT. Worker productivity and the nutritional status of Kenyan road construction laborers. Am J Clin Nutr 1982; 36: 68—78.
4. Basta SS, Soekirman, Karyadi D, Scrimshaw NS. Iron deficiency anemia and the productivity of adult males in Indonesia. Am J Clin Nutr 1979; 32: 916—925.5:e888.
5. Borm GF, Fransen J, Lemmens WAJG. A simple sample size formula for analysis of covariance in randomized clinical trials. Journal of Clinical Epidemiology. 2007 60 1234-1238
6. Kahan BC, Morris TP. Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. BMJ 2012;345:e5840.

14. APPROVAL

Senior Statistician	Jin Ling	
Chief Investigator	Nathan Congdon	