Gatekeeper training for vendors to reduce pesticide self-poisoning in rural South Asia

Statistical Analysis Plan

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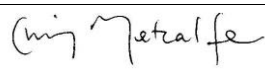
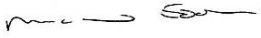
Authorising Statistician	Chris Metcalfe	Professor of Medical Statistics, University of Bristol		03/10/2023
Chief Investigator	Michael Eddleston	Professor of Clinical Toxicology, University of Edinburgh		03 OCT 2023

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Abbreviations

CI	Confidence Interval
CONSORT	Consolidated Standards for Reporting Trials
COVID-19	Coronavirus Disease 2019
DMC	Data Monitoring Committee
ICH	International Conference on Harmonisation
PYRS	Person-years of follow-up
SAP	Statistical Analysis Plan
SMS	Short Messaging Service

1. INTRODUCTION & PURPOSE

The statistical analysis plan (SAP) for the Vendor study has been written in accordance with the CONSORT statement, and International Conference on Harmonisation (ICH) Statistical Principles for Clinical Trials E9. The SAP details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from the Vendor study, for presentation in the main results papers.

The purpose of the plan is to:

Ensure that the analysis is appropriate for the aims of the trial, reflects good statistical practice, and that interpretation of a priori and post hoc analyses is appropriate.

Explain in detail how the data will be handled and analysed to enable others to perform the actual analysis in the event of sickness or other absence.

Additional exploratory or auxiliary analyses of data not specified in the protocol are permitted but fall outside the scope of this analysis plan (although such analyses would be expected to follow Good Statistical Practice including being labelled as post hoc, as appropriate, in any publication).

The analysis strategy will be made available if required by journal editors or referees when the main paper(s) are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with this analysis plan, but if reported the source of such a post-hoc analysis will be declared.

Amendments to the statistical analysis plan will be described and justified in the final report of the trial.

2. SYNOPSIS OF STUDY DESIGN AND PROCEDURES

The following is a brief outline of the study design, based on the published protocol[1], with the sole purpose of informing the statistical analysis plan. For other purposes, the current version of the study protocol should be referred to.

2.1 Trial objectives and aims

In Sri Lanka, pesticide shops are widely spread in agricultural areas and pesticides are freely available for purchase over the counter, allowing their easy accessibility for self-poisoning. Our earlier research suggested that preventing sales of pesticides to non-farmers and intoxicated persons in areas with high rates of self-poisoning, by using a ‘gatekeeper’ approach, is potentially cost-effective in reducing pesticide self-poisoning.[2]

We tested the hypothesis that gatekeeper training for pesticide vendors prevents pesticide self-poisoning without increasing the incidence of other forms of self-harm.

2.1.1 Primary objective

- To test the effectiveness of a gatekeeper training intervention for pesticide vendors to prevent pesticide self-poisoning.

2.1.2 Secondary objectives

- To determine whether the intervention results in “method substitution”.
- To assess vendor attitudes to the training.

- To compare costs of training vendors with treatment costs of poisoned patients to assess the cost-effectiveness of introducing vendor training (health economics analysis plan described separately).

2.2 Trial design & setting

This is a community based, stepped wedge cluster randomised controlled trial. The trial is taking place across two areas of Sri Lanka; North Central Province (Anuradhapura and Polonnaruwa; study zone 1), and an "expansion area" (Matale, Batticaloa, Trincomalee, Vavuniya and part of Ampara; study zone 2).

2.3 Entry criteria for the intervention

All pesticide shops and vendors directly involved in pesticide sales in the study area during the study period are eligible for the intervention. Vendors who are aged under 18 years (<1%) are excluded, as well as cashiers and other store workers in larger pesticide shops who do not directly interact with pesticide-purchasing customers.

2.4 Description of interventions

The intervention involves training pesticide vendors to identify a person at high-risk of self-poisoning with the pesticide they wish to purchase (gatekeeper function at the point of sale) and to then refuse to make a sale (means restriction). Its form is based on the pilot study,[3] and consists of a 1-hour discussion with vendors on their experience with customers who had self-poisoned with pesticides shortly after purchasing them, followed by a 1-hour interactive presentation on how to identify and respond to high risk customers. Vendors are trained to observe customer behaviour, check for intoxication, and ask questions which farmers would be expected to know the answer. Role play exercises were used to consolidate the training. Short films were used to standardise presentation of information and training. During the COVID-19 pandemic training sessions were often delivered remotely.

Brief follow-up training is provided at 6-12-month intervals to reinforce the lessons learnt during training. An assessment of fidelity occurs at this point. Reminders are sent out by short text messages (SMS) at regular intervals to remind shopkeepers of the training's key messages.

Checks for the establishment of new pesticide shops in the study area were made every 6 months, primarily by discussion with key local contacts. Checks for new staff are made via SMS with shops that have been trained.

The comparison is with outcome episodes during the usual practices of shops prior to introduction of the intervention.

2.5 Randomisation procedures

The unit of randomisation in this study is a cluster of two to five neighbouring divisions. These groupings were pre-specified based on proximity and likely risk of contamination due to the presence of shops on/close to adjoining borders. In other words, if the risk of contamination between neighbouring divisions was high, they were grouped together and the intervention introduced into these divisions at the same time. The clusters were placed in a random order (using Stata statistical software: StataCorp, College Station, Texas, 2017) and the intervention rolled out to each cluster in turn following this random sequence.

In zone 1's 29 divisions, the intervention was initially introduced at approximately 76-day intervals; this was reduced to 67-day intervals following COVID-19 pandemic lockdown in March to June 2020. In zone 2's 41 divisions, the intervention was initially planned to be introduced at 66-day intervals. However, as zone 2 started later, after the lockdown the intervention was introduced at 42-day intervals. Zone 2 intervals are shorter to ensure all training is completed by the time that zone 1 training is complete. Before the first intervention, a monitoring period (160 days in zone 1 and 61 days in zone 2) was established, during which a baseline number of pesticide self-poisoning episodes were recorded. Overall, the intervention is being rolled out in 15 steps in zone 1 over 39 months and in 16 steps in zone 2 over 23 months. The observation period concluded with an extended step once the intervention had been introduced in all areas.

2.6 Eligibility criteria for the population

There are no minimum or maximum age limits for inclusion. Non-residents of the study area (i.e. who cannot be linked with a specific study cluster) are excluded from the final analysis.

2.7 Outcome measures

2.7.1 Primary outcome

- Fatal and non-fatal pesticide self-poisoning episodes (including recurrent episodes for an individual) amongst the resident population of the study area, identified from surveillance of hospitals and police stations during the study period.

2.7.2 Secondary outcomes

- Pesticide self-poisoning episodes (fatal and non-fatal episodes) presenting to study hospitals or identified through police stations who used pesticides purchased within 24 hours of the act.
- Hospital-presenting self-harm episodes involving any method of self-harm.
- Suicides involving any method of self-harm.

2.8 Sample size and justification

The primary outcome measure is fatal and non-fatal pesticide self-poisoning episodes amongst the entire resident population of the study area. However, the intervention is directed towards a subpopulation of 'shop cases' who self-poison using pesticides bought for this purpose from a shop in the preceding 24 hours. The subpopulation affected by the intervention is likely to be about 20% of all primary outcome episodes.[4 5] We aim to identify any effect of the intervention on all primary outcome events in the whole population.

Initially, the study was powered taking the mean division population of 15+ year-olds to be 35 000, the rate of pesticide self-poisoning without intervention to be 250 episodes per 100 000 person-years and the coefficient of variation in rates of pesticide self-poisoning across the divisions to be 0.55 (calculated from our ongoing provincial and study area hospital surveillance). In this case, a stepped-wedge design with the intervention introduced into 29 divisions in two districts at each of 15 steps separated by 78 days (7479 person-years of follow-up of each district at each step) would detect a true 11.5% reduction to 221 episodes per 100 000 person-years with 90% power at the 5% significance level. To achieve this 11.5% reduction overall requires a 58% reduction

among shop cases, assuming shop cases make up 20% of all episodes in the absence of the intervention. A smaller 10% reduction would be detected with 80% power, all else being equal.

However, after 6 months, the rate of pesticide self-poisoning in the study area was observed to be 130 episodes per 100 000 person-years. To achieve an acceptable level of statistical power with this lower incidence rate we expanded into an additional study area. Assuming for zone 2 that the intervention would be introduced into 41 divisions in four districts at each of 15 steps each of 66 days' duration, then for zones 1 and 2 combined (with an average 6750 person-years of follow-up of each district during each step) a 11.5% reduction from 130 to 115 pesticide self-poisoning episodes per 100 000 person-years would be detected with 88% power at the 5% significance level.

3. GENERAL ANALYSIS CONSIDERATIONS

3.1 Data collection and analysis populations

We established a prospective surveillance system to identify all inpatient self-harm episodes reported to study hospitals and police stations.

In zone 1, surveillance data collection started on 1 April 2019 and the training intervention started on the 30th September 2019. In zone 2, data collection started on 1 November 2020 and the training intervention starting on the 18th January 2021. Surveillance closes in both zones on 30th September 2023. Surveillance researchers record all fatal and non-fatal self-harm episodes admitted to the wards of 120 study hospitals across the region. Following our previous household pesticide storage study processes,[6] researchers prospectively record self-harm patients through frequent visits to small primary hospitals (7–80 beds), at least weekly, and by telephone calls from hospital staff when patients are admitted. In secondary and tertiary care hospitals, researchers attend the medical wards daily and other wards at least weekly to identify patients with other (less common) non-poisoning means of self-harm in surgical, paediatric and intensive care units, as well as morgues. During the study set-up, we explored where study area patients presented to hospital and ensured that all accessed hospitals were surveyed, both in and out of the study area.

Data collected include demographic data for all self-harm episodes (sex, date of birth, place of residence and farming status) and episode-specific information (date and time of self-harm event, method of self-harm, whether the individual was alcohol intoxicated, time of hospital admission and whether the individual died). For pesticide poisoning episodes, additional data are collected on how the individuals accessed pesticides (whether they bought the pesticides from a shop or accessed them from home or nearby). Specific information collected for shop cases includes whether the individual or someone else bought pesticides, the individual's intent at the time of pesticide purchase (self-harm or agricultural purpose), date and time of the pesticide purchase and the division location of the pesticide shop.

We record all self-harm deaths occurring outside hospital settings through a network of 90 police stations and judicial medical officers. The researchers visit these sources every 3 months to extract data about self-harm events, namely the home address, method of self-harm and the source of any pesticide used. Where patients leave hospital before they can be interviewed or non-hospitalised deaths occur, address details of the individuals are obtained from the hospital or police station and permission requested from the patient or family to interview them in their homes about the source of pesticide used in the poisoning.

The divisional residence of the patient and date of self-harm event is used to allocate episodes to the correct study arm.

3.2 Statistical software

The intention is that the current version of Stata Statistical Software (StataCorp, College Station, Texas) is used for all analyses. However, in the event that the analysis models will not converge, an attempt would be made with specialist software such as MLWin.

4. DESCRIPTION OF PARTICIPANT CHARACTERISTICS

4.1 Disposition

The flow of clusters through the trial will be summarised in a CONSORT diagram as adapted to stepped wedge cluster randomised trials; see Section 7.

5. ANALYSIS OF EFFECTIVENESS

5.1 Primary analysis

The primary analysis will follow the intention-to-treat principle and will test the null hypothesis of no difference in observed population incidence of self-poisoning with pesticides between periods/clusters with and without the intervention in place.

A mixed effects Poisson regression model will be used to estimate the effect of the intervention as an incidence rate ratio, alongside associated 95% confidence interval and p-value.[7] Variation in outcome between clusters will be accounted for by the inclusion of a random effect for cluster with appropriate distribution. Any longer-term time trends in outcome events will be accommodated by the inclusion of one or more time functions, e.g. periodic regression if seasonality is apparent, and fractional polynomials for secular trends.[8] Typically, peak months for pesticide application are May, June, July (Yala season), October, November and December (Maha season).

The analysis model is as follows:

$$\log(\lambda_{ij}) = \lambda_0 + f_j(season) + f_j(secular) + \beta_1 x_{1ij} + z_i + e_{ij}$$

Where:

$\log(\lambda_{ij})$ is the event rate in cluster *i* during step *j*

λ_0 is the base event rate

β_1 is the treatment effect estimate

x_{ij} is the intervention status of cluster *i* during step *j*, 0=pre-intervention, 1=post-intervention

z_i are random effects for the clusters *i*, with distribution $N(0,\sigma_z)$

e_{ij} are the errors from the model, for cluster *i* in step *j*, with distribution $N(0,\sigma_e)$

The primary analysis consider clusters to be post-intervention at the start date of the step when vendor training commences in the cluster. Because involvement of the two zones started at

different times, they are run as parallel studies. The analysis will be conducted separately for each zone, and estimates then pooled using a fixed-effect meta-analysis approach.

Compliance with model assumptions will be checked. For example, if there is a greater than expected number of clusters reporting no episodes of pesticide self-poisoning, then use of a zero-inflated model will be explored. If a normal distribution is a poor fit to the variation of rates across clusters, other distributions such as the gamma distribution will be considered for the random effect.

If the model fails to converge then robust standard errors will be used to account for clustering in place of a random effect.

5.2 Secondary analyses

The same analytical approach as used for the primary analysis will be adapted to each of the secondary outcomes.

5.3 Sensitivity analysis

The primary outcome analysis will be repeated but with the date on which intervention training was completed being the date on which a cluster moves from the control condition to the intervention condition.

The analysis of episodes following a pesticide purchase will be repeated for self-poisoning within 48 hours of the purchase.

5.4 Pre-specified sub-group analyses

Pre-specified sub-group analyses will investigate whether the effectiveness of the intervention is different in (i) the two study zones, and (ii) between clusters with a lower and higher number of pesticide shops, included in the analysis as the trend over quintiles of the number of pesticide shops.

5.5 Exploratory/other analysis

Time-series graphics will be presented for each of the two study zones, showing, month by month, the occurrence of primary outcome events over the study period, with the timing of significant national events indicated (COVID-19 lockdowns, pesticide import ban, economic crisis). This study has been conducted during an exceptionally turbulent time for Sri Lanka, preventing the pre-specification of sensitivity analyses to gauge the impact of these events on intervention effectiveness, any such sensitivity analyses will be exploratory and based upon the impact on self-poisoning episodes overall.

Summary statistics will be presented on self-poisoning episodes using pesticides bought in the previous 24 hours, in particular whether the shop at which the pesticides were purchased (when known) was within the individual's cluster of residence, and whether the individual was a member of one of the target risk groups of non-farmers and intoxicated at the time of attempted purchase.

The rates of primary outcome events, and of self-poisoning episodes using pesticides bought in the previous 24 hours will be examined over time with reference to the time at which the intervention was introduced in a cluster. Whether there is evidence of a diminishing effect of the intervention with time will be considered.

6. STUDY CONDUCT

6.1 Trial committees

The trial management group will oversee the conduct and progress of the study.

An independent Data Monitoring Committee (DMC) oversees the safety of trial participants and collection of high-quality data: Prof John Norrie (Professor of Medical Statistics and Trial Methodology, University of Edinburgh, Chairperson), Prof Saroj Jayasinghe (Professor of Medicine, University of Colombo), and Prof Richard Maude (Professor of Tropical Medicine, University of Oxford).

6.2 Adverse events

Adverse events judged to be due to the intervention will be described in the primary results paper

7. OUTLINES OF CONSORT FLOWCHART AND RESULTS TABLES

FIGURE: CONSORT Flowchart format. A separate flowchart will be presented for each zone

	CLUSTER 1 Popn=??K CLUSTER 2 Popn=??K	CLUSTER 3 Popn=??K CLUSTER 4 Popn=??K	CLUSTER 5 Popn=??K CLUSTER 6 Popn=??K	CLUSTER 7 Popn=??K CLUSTER 8 Popn=??K	CLUSTER 9 Popn=??K CLUSTER 10 Popn=??K
START 19/08/2019					
STEP 1 DD/MM/YYYY	Vendors trained [1] ??/?? [2] ??/??				
STEP 2 DD/MM/YYYY		Vendors trained [1] ??/?? [2] ??/??			
STEP 3 DD/MM/YYYY			Vendors trained [1] ??/?? [2] ??/??		
STEP 4 DD/MM/YYYY				Vendors trained [1] ??/?? [2] ??/??	
STEP 5 DD/MM/YYYY					Vendors trained [1] ??/?? [2] ??/??
CLOSE DD/MM/YYYY					

TABLE: Treatment effect estimates

Outcome measure	Number of events	PYRS follow-up	Rate per 10K PYRS	Rate ratio (95% CI)	p-value
PRIMARY OUTCOME ANALYSIS[1]					
All self-poisoning					
Intervention					
Comparison					
SUBGROUP ANALYSIS[2]					
All self-poisoning in Zone 1					
Intervention					
Comparison					
All self-poisoning in Zone 2					
Intervention					
Comparison					
SENSITIVITY ANALYSES					
All self-poisoning					
Clusters switched to intervention once training complete					
Intervention					
Comparison					
SECONDARY ANALYSES					
Self-poisoning with pesticides bought in previous 24 hours					
Intervention					
Comparison					
All hospital-presenting non-fatal self-harm					
Intervention					
Comparison					
All fatal self-harm					
Intervention					
Comparison					

NOTES: [1] A risk difference for the comparison of intervention to control on the primary outcome will be presented in the text. [2] The p-value for the test of the null hypothesis, equal treatment effect in the population for Zone 1 and Zone 2 will be presented in the text.

8. REFERENCES

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