Metcalfe, C., Eddleston, M., & Dobbins, T. A community trial to determine whether 'safe storage' reduces pesticide self-poisoning in rural Asia: Statistical Analysis Plan

A community trial to determine whether `safe storage' reduces pesticide self-poisoning in rural Asia

Statistical Analysis Plan

Version 1.0 (20 July 2016)

The following people have reviewed the Statistical Analysis Plan and are in agreement with the contents			
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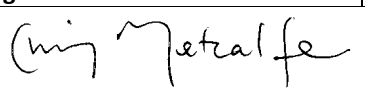
Chris Metcalfe University of Bristol	Author & study statistician		4 Aug 2016
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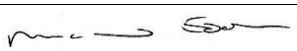
Michael Eddleston University of Edinburgh	Chief Investigator		23 Aug 2016

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1. INTRODUCTION & PURPOSE

This document details the rules proposed and the presentation that will be followed, as closely as possible, when analysing and reporting the main results from *"A community trial to determine whether `safe storage' reduces pesticide self-poisoning in rural Asia".*

The purpose of the plan is to:

1. 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 respectively is appropriate.
2. 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).

The analysis strategy will be made available if required by journal editors or referees when the main papers are submitted for publication. Additional analyses suggested by reviewers or editors will, if considered appropriate, be performed in accordance with the 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 an outline of the study design abstracted from the published protocol paper (Pearson et al, 2011) with the sole purpose of informing the statistical analysis plan. The current version of the study protocol always takes precedence over this summary.

2.1. Trial objectives and aims

Pesticide self-poisoning is a major public health and clinical problem in rural Asia. One approach to reducing access to pesticides is for households to store pesticides in lockable "safe-storage" containers. We aim to evaluate the effectiveness of this approach in an adequately powered and well-designed randomised controlled trial.

2.1.1. Primary objective

To determine whether the introduction of safe storage boxes to households where pesticides are used or stored will reduce the incidence of pesticide self-poisoning.

2.1.2. Secondary objectives

- To determine whether the prevention of pesticide self-poisoning with safe storage boxes results in any degree of "method substitution", i.e. an increase in self-harm using other methods.
- To determine whether the safe storage boxes decrease (due to secure storage) or increase (due to encouraging storage nearer the home) the number of accidental pesticide poisonings, in both adults and children.

2.2. Trial design and configuration

This is a community-based, cluster randomised controlled trial (RCT) of safe storage containers.

2.3. Trial setting

The trial is taking place in the Anuradhapura district of Sri Lanka's North Central Province (population 1,104,664: Census 2001). Villages were recruited from the Mahaweli H region, including the divisional secretariats of Thambuttegama, Talawa, Galnewa, Rajanganaya and Nochchiyagama. The study area was divided into ten bands, each roughly corresponding to about half of a divisional secretariat, the baseline survey and household recruitment taking place in each band in turn.

2.4. Eligibility criteria

2.4.1. Inclusion criteria

All villages within the five divisional secretariats were eligible for study entry except those recruited to our previous pilot studies. Within recruited villages, those households in the intervention arm where pesticide use or storage was reported were eligible for a lockable safe storage box.

2.4.2. Exclusion criteria

Households where there was no adult available to provide consent were excluded.

2.5. Description of interventions

The intervention was a safe storage container made from UV-resistant plastic that can be placed outside the house (in the home garden or field) and partially buried underground. The container has two lids: an inner lid that can be locked and an outer lid to protect the

lock against weather or soil damage. On delivery a short demonstration of appropriate use was given, with help available to bury the device if required.

The comparison is with usual practice in the storage of pesticides in this region.

2.6. Randomisation procedures

Clusters (a village or pair or small group of adjoining villages where boundaries were blurred) were the randomisation unit and were allocated to either the intervention or comparison group. Large imbalances between study arms in the number of allocated clusters, the number of people in households eligible for a box, and the previous history of pesticide self-harm in the cluster, were avoided by the method of minimisation. The allocation of each cluster in turn was random, but with a greater chance of the allocation which achieved the better balance on minimisation variables between trial arms.

The study area was partitioned into ten “bands” (geographical areas), with the baseline survey being completed for one band at a time. Once the survey had been completed for all clusters in a band, the clusters in that band were randomly allocated to the intervention and comparison groups. Concealment of allocation was ensured by securing agreement to participate, and completing the baseline survey, prior to random allocation of clusters within a band.

2.7. Sample size and justification

Our previous research has found the incidence of pesticide self-poisoning in the district to be approximately 175 per 100,000 per year, or 525 per 100,000 over the three years of the study. We hypothesised that provision of the lockable containers would lead to a reduction in pesticide self-poisoning by 33% from 175/100,000 to 117/100,000. At 80% power and 5% type I error rate, a total of 68,676 person years of follow-up were required in each arm of the study to detect a true intervention effect of this size.

Our previous data on this region suggested that a design effect of 1.75 would accommodate variation in self-harm rates between clusters. This indicated that 120,183 person years were required in each arm of the trial, or 40,061 individuals must be followed for an average of three years.

Some households within intervention clusters did not use pesticides (and therefore were not offered a container), while others did not use their container (non-compliance). Some households within control clusters may have acquired a lockable container (contamination). If 20% of individuals in the intervention arm live in a household not using a lockable container, and 5% of individuals in the control arm live in a household using a lockable container, then 217,944 person years of follow-up were required in each arm of the trial to compensate, an overall target of 48,432 households.

As planned (see Pearson et al, 2011), the assumptions behind this sample size target were compared to the emerging baseline data in October 2012, and reviewed by the data monitoring committee in February 2013. This indicated that the study would have sufficient statistical power.

Once the sample size target had been achieved, recruitment continued to complete the final geographical area. This resulted in just short of 55,000 households being recruited in 181 clusters, exceeding the target of 48,000 households in 162 custers suggested by our sample size calculation.

2.8. Blinding

It was important to keep the outcome recorders blind to the allocation of a case's cluster of residence. The trial management group received regular accounts of the processes outcome recorders followed in order to match cases to an individual or household in the baseline database, and review any activities which may lead to unblinding.

Likewise, members of the consensus committee (see below section 2.9) convened to judge the likelihood that difficult to code cases were acts of self-harm, were provided with information without indication of whether a case was resident in an intervention or comparison cluster.

Clinical staff in the local hospitals were not told which clusters were in the intervention and comparison groups, although they may have been aware in some cases.

2.9. Trial committees

An independent Data Monitoring Committee (DMC) was established for the trial. Analyses required by the DMC will be provided by the trial statistician in strict confidence.

At completion of the study, an expert committee will consider cases of pesticide poisoning for which it is unclear whether these were deliberate or accidental. This committee will be blind to the allocation of each case's cluster of residence.

2.10. Outcome measures

2.10.1. Primary outcome

The incidence of deliberate pesticide self-poisoning, both fatal and non-fatal, amongst people aged 14 years or older, over the three years study period.

2.10.2. Secondary outcomes

- The incidence of pesticide poisoning in general (deliberate and accidental, of all ages)

- Non-fatal self-harm (all methods), individuals aged 14 years+
- Fatal self-harm (all methods), individuals aged 14 years+
- Self-poisoning (all substances), individuals aged 14 years+
- Pesticide poisoning in children (younger than 14 years)
- Incidence of non-pesticide fatal and non-fatal self-harm in individuals aged 14 years+ to detect evidence of method substitution and the specific methods people use to replace pesticides

3. GENERAL ANALYSIS CONSIDERATIONS

3.1. Analysis populations

The primary analysis population will be the residents of clusters randomly allocated to the safe storage intervention or to the comparison arm. We know from our baseline survey that some individuals spend only part of the year living in the study area (those travelling abroad to work for example) and have tried to obtain an indication of how long each year they are resident in a household.

Other individuals live in more than one household over the course of the year, and this may be in two different study areas potentially randomised to different arms of the study. Again we have attempted to obtain an indication of how long during each year the individual is resident in each household; for both groups this will allow us to better estimate the true person years of exposure. For this latter group, if an outcome event does occur, then, in the absence of information on which household they are resident in at the time, the self-harm episode will be linked to the individual's household (and corresponding study arm) closest to the hospital they present to. This is a pragmatic approach for what appears to be a small group of study participants.

Finally, there will be the normal influx and outflow from the study area. However, to calculate the person-years of exposure from the cross-sectional baseline survey data we have, we will assume a constant resident population over the three years of the study. Supplementary data on migration will be investigated to assess the plausibility of the assumption of a constant population size.

3.2. Linking outcome events to the baseline survey data

The minimum needed for an outcome event to be included in the primary analysis is for the patient to be matched back to their cluster of residence. This level of matching has, as of May 2015, been achieved for 2258/2275 eligible cases (99.25%).

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 cluster randomised trials (Campbell et al, 2004) that will include the eligibility, reasons for exclusion, numbers randomised to the two treatment groups, losses to follow up and the numbers analysed, supplemented by the mean number of residents per cluster at each stage.

4.2. Baseline characteristics

Summary data at the cluster (i.e. the randomisation units), household and individual levels will be presented by study arm. Details are given in section 8.1 below.

5. ASSESSMENT OF STUDY QUALITY

5.1. Compliance

It is impractical, and likely to affect use, to monitor appropriate use of the storage boxes across the extensive study area. Utilisation of the boxes was the subject of a sub-study involving 5 clusters. The resulting data will help with the interpretation of, but not be a part of, the main trial analysis. The clusters taking part in this sub-study will be excluded in a sensitivity analysis - see later.

5.2. Extent of study intervention

The number of households eligible for a box in each intervention cluster, and receiving one, has been recorded, and will be presented in summary form in the main study paper.

5.3. Protocol deviations

These were recorded, reported and addressed as appropriate, in line with the intention to treat principle followed by the primary analysis.

6. ANALYSIS OF EFFECTIVENESS

6.1. Primary analysis

The primary analysis will follow the intention-to-treat principle, and will test the null hypothesis of no difference in the population incidence of self-poisoning with pesticides

between clusters allocated to the safe storage intervention and clusters in the usual practice comparison arm.

The three-year follow-up period will begin on the same date for all clusters in a recruitment band, that date being the day on which the distribution of safe storage devices started in that band. As distribution took several months within some bands, this means that some intervention clusters were without the safe storage boxes for the early weeks of their follow-up, thereby diluting the observed effect during that period.

A Poisson regression model will be employed, with standard errors inflated to accommodate clustering by cluster. This inflation will be achieved using a normal or gamma distributed random effect, whichever best describes the variation in pesticide self-poisoning across villages. This primary analysis will be adjusted for the minimisation variables used in the random allocation (number of people in households eligible for a box, previous history of pesticide self-poisoning in the cluster). Tertiles will be defined for these two variables, and any pattern of pesticide self-poisoning across the three categories accommodated by including them in the regression model as two dummy variables in each case.

The null hypothesis for the primary analysis is "no difference between randomly determined intervention and control groups in deliberate pesticide self-poisoning, both fatal and non-fatal, amongst people aged 14 years+, over the three-year study period". The following Poisson regression model (1) regresses rates λ_p for each cluster *p* on covariates x_{1p}, the allocated intervention group, $x_{2(2)p}$ and $x_{2(3)p}$, distinguishing tertiles of number of people in households eligible for a box, and $x_{3(2)p}$ and $x_{3(3)p}$, distinguishing tertiles of previous pesticide self-poisoning in the village.

$$\log(\lambda_p) = \lambda_0 + z_{0p} + \beta_1 x_{1i} + \beta_2 x_{2(2)p} + \beta_3 x_{2(3)p} + \beta_4 x_{3(2)p} + \beta_5 x_{3(3)p}$$
$$z_{0p} \sim D(0, \sigma_p) \qquad (1)$$

Variation in outcome between clusters is accommodated as standard deviation σ_p of a level 2 zero mean random effect (normal or gamma distribution as stated above). The estimated risk ratio for the intervention effect, $e^{\beta 1}$, will be presented with 95% confidence interval and p-value.

Allowance will be made if a greater than expected number of clusters without a case of pesticide self-poisoning is observed, using the Stata "zinb" (zero-inflated negative binomial regression) command for instance, which includes a test of whether this approach offers an improvement over the standard model. If it is not possible to accommodate the between-cluster variation in outcome as a random effect, a non-parametric robust standard error approach will be adopted (as described in Section 30.4 of Kirkwood & Sterne, 2003).

6.2. Secondary analyses

The primary analysis will be adapted to each of the secondary outcome measures in turn.

6.3. Sensitivity analysis

Four sensitivity analyses will be undertaken:

[1] The primary analysis will be repeated after excluding the five intervention arm clusters where sub-studies (of safe storage box usage for example) are undertaken. Participation in these sub-studies may affect household compliance with the safe storage intervention.

[2] A further sensitivity analysis will investigate the effect of the approach taken with individuals living in more than one household over the course of the year (see Section 3.1). The sensitivity analysis will analyse the data with these individuals in the household within which they were resident during the baseline survey period for the corresponding cluster (where relevant, this will be the first time the individual was captured in the survey).

[3] The primary analysis will be repeated with the three-year follow-up period for each intervention cluster starting on the date that distribution of the safe storage devices began for that cluster (rather than when distribution started in the band as a whole, as in the primary analysis).

[4] The primary analysis will be repeated based on “definite” primary outcome events, i.e. not including those events which had to be considered by the expert committee.

6.4. Pre-specified sub-group analyses

Pre-specified sub-group analyses will investigate whether the effectiveness of the safe storage intervention is modified by:

- the cluster-level historical rate of pesticide self-poisoning (baseline survey)
- the proportion of households reporting a problem alcohol (baseline survey)
- the proportion of households provided with a locked box
- the time since boxes were distributed to the band

This analysis will be based on interaction terms, generated as the product of the cluster allocation (1 = safe storage intervention, 0 = comparison) and sub-groups defined as tertiles of the variables (0 = low, 1 = medium, 3 = high, or first, second, third year of follow-up). The interaction term will be added to the model for the primary analysis as two dummy variables, hence giving two degree of freedom tests of the null hypotheses, no modification of the effect of the safe storage intervention by (i) cluster-level historical rate of pesticide self-poisoning, (ii) proportion of households in a cluster reporting a problem with alcohol, (iii) proportion of households in a cluster provided with a locked box, (iv) time since distribution of boxes began in the band.

7. ADVERSE EVENTS

Adverse events judged to be due to the storage device will be described in the primary results paper.

8. FINAL REPORT TABLES AND FIGURES

Table 1. Baseline characteristics of households and individuals by randomised group

	Intervention	Comparison
Number of clusters		
Number of households		
Number (%) of households eligible for a locked box		
Number (%) of households eligible for a locked box & receiving one		
Number (%) of households reporting a case of pesticide self-harm		
Number (%) of households reporting a case of problem alcohol use		
Household construction:		
Number (%) solid construction, durable materials		
Number (%) semi-permanent construction, mixture of materials		
Number (%) improvised construction, non-durable materials		
Household possession of motorised vehicle:		
Number (%) four wheels (car, tractor)		
Number (%) two to three wheels (motorbike)		
Number of individuals aged 14 years+		
Number (%) of females aged 14 years+		
Number of individuals aged <14 years		
Mean age in years (standard deviation)		
Number (%) of individuals aged 14 years+ in households eligible for a locked box, and resident there:		
All year round		
7 – 11 months		
1 – 6 months		
<30 days		

Table 2. Primary and secondary poisoning event-based outcomes summarised as number of events (n events), person-years (PYRS) follow-up (FU), and rate per 10,000 person years (rate/10^4) with rate ratio (RR) and 95% confidence interval (CI) comparing intervention to control groups*

	n events	PYRS FU	Rate / 10^4	RR	95% CI	p-value
PRIMARY: Pesticide self-poisoning (14 years+)						
Intervention						
Comparison						
All pesticide poisoning, deliberate and accidental (all ages)						
Intervention						
Comparison						
Pesticide poisoning in children (<14 years)						
Intervention						
Comparison						
Self-poisoning, all substances (14 years+)						
Intervention						
Comparison						
Non-fatal self-harm, all methods (14 years+)						
Intervention						
Comparison						
Fatal self-harm, all methods (14 years+)						
Intervention						
Comparison						
Non-pesticide non-fatal self-poisoning (14 years+)						
Intervention						
Comparison						
Non-pesticide fatal self-poisoning (14 years+)						
Intervention						
Comparison						

* Rate ratio estimates are adjusted for the number of people per cluster in households eligible for a box, and baseline pesticide self-poisoning rate per cluster

Table 3. Sub-group analyses by primary outcome events summarised as rate per 10,000 person years (rate/10^4) for each sub-group within the intervention and comparison groups, with the relative rate ratio (RRR) and 95% confidence interval (CI) comparing the intervention effect between subgroups. The p-value is from a likelihood ratio test comparing models with and without the interaction terms.

	Rate / 10^4 intervention	Rate / 10^4 comparison	RRR	95% CI	p-interaction
Cluster historical rate of pesticide self-poisoning					
Tertile 1					
Tertile 2					
Tertile 3					
Proportion of households in cluster reporting alcohol problems					
Tertile 1					
Tertile 2					
Tertile 3					
Proportion of households in cluster provided with locked box					
Tertile 1					
Tertile 2					
Tertile 3					
Time since distribution of locked boxes to cluster					
Year 1					
Year 2					
Year 3					

* Relative rate ratio estimates are adjusted for the number of people per cluster in households eligible for a box, and baseline pesticide self-poisoning rate per cluster

Figure 1. CONSORT chart

Figure 2. Cumulative incidence of pesticide self-poisoning in intervention (solid line) and comparison (dashed line) groups

Supplementary material

Table S1. Methods of self-harm other than self-poisoning, all involving individuals aged 14 years or older, fatal and non-fatal combined

	n events	PYRS FU	Rate / 10^4
Hanging			
Intervention			
Comparison			
Self-cutting			
Intervention			
Comparison			
Self-burning			
Intervention			
Comparison			
Other			
Intervention			
Comparison			

9. REFERENCES

Campbell MK, Elbourne DR, Altman DG, for the CONSORT Group. (2004). CONSORT statement: extension to cluster randomised trials**. BMJ 328:** 702-8.

Kirkwood BR, Sterne JAC. (2003). **Essential Medical Statistics. 2nd Edition.** Oxford: Blackwell.

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