Investigating interventions to increase uptake of HIV testing and linkage into care or prevention for male partners of pregnant women in antenatal clinics in Blantyre, Malawi: an adaptive Phase II multi-arm multi-stage cluster randomised trial (ISRCTN18421340)

Statistical Analysis Plan

(Linked to Protocol v0.5; 03/06/2016)

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1. **Overview of study design, setting and recruitment**

   The aim of this cluster randomised trial (CRT) is to investigate whether providing HIV self-test kits alone or with an additional intervention through pregnant women who are accessing antenatal care (ANC) for the first time can increase male partner HIV testing and linkage into HIV treatment or prevention services. This is a Phase II trial intended to investigate safety outcomes, to provide an estimate of acceptability to the woman and efficacy relating to uptake of testing and subsequent HIV services by the male partner. The trial involved testing 5 different interventions for improving linkage to the “male friendly” clinic regardless of male partner HIV result including financial incentives and reminders compared to the standard of care (SOC) of giving a personalised letter only to the male partner (annex - Fig. 1). The trial is a multi-arm multi-stage (MAMS) adaptive design with 6 arms (5 intervention and 1 SOC) in the first stage with a planned interim analysis at the end of that stage of recruitment aiming to drop arms and re-calculation of sample size. Enrolment continued in stage two and analysis conducted for participants enrolled into stage two, as well as combing effect estimate across the two stages, where appropriate.

2. **Outcomes**

   **Primary outcome**

   1) The proportion of male partners of ANC attendees who test for HIV and link into HIV care or prevention within 28 days of enrolling the woman.

   **Secondary outcomes**

   1) Proportion of male partners of ANC attendees who test for HIV within 28 days.
   2) Proportion of women who accept to participate in their allocated study arm.
   3) Risk of serious adverse events within 30 days of enrolment associated with each study arm.
   4) Total cost of implementing the service per study arm.

   **Adverse events and safety reporting:**

   Adverse events will be reported using terms and definitions outlined below

   - **Grade 3 events, any of the following within 30 days:**
     - Intimate partner violence that leads to pain, bruising or marks within 24hrs.
     - Threat of life-threatening violence (e.g. statement of intent to kill, mock strangulation, threatened with a knife or gun
     - Physically coercive sex
     - Reports fearing for her life
     - Marriage break
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• Grade 4 events, any of the following within 30 days:
  o Intimate partner violence leading to hospitalisation or death
  o Suicide or attempted suicide
  o Attack using potentially lethal force (e.g. knife, gun, hammer, kicks to the head)

• Grade 5, death.

3. Randomisation

Block randomisation was used to allocate the ANC days across the trial arms in either trial stage. Although recruitment was done from three PHCs no stratification was applied because the PHCs are very similar. The allocation sequence was only communicated to the field workers on the day of recruitment to minimise selection bias.

4. Description of each trial arm

1) Standard of care (SOC): Women will receive personalised letters to give their male partners inviting them to come to the male friendly clinic.

2) Self-test kits only: Women receive a letter and self-test kits to deliver to their male partners.

3) Self-test kits + a $3 financial incentive: Women receive a letter and self-test kits to deliver to their male partners who will get an incentive of $3 conditional on attending the male friendly clinic.

4) Self-test kits + a $10 financial incentive: Women receive a letter and self-test kits to deliver to their male partners who will get an incentive of $10 conditional on attending the male friendly clinic.

5) Self-test kits + lottery incentive: Women receive a letter and self-test kits to deliver to their male partners who will be entered into a lottery with a 10% chance of winning $30 conditional on attending the male friendly clinic.

6) Self-test kits + phone call reminder: Women receive a letter and self-test kits to deliver to their male partners who will receive up to two phone calls to remind them to test and link into male friendly clinic to receive HIV care or HIV prevention services.

5. Sample size justification

Sample size for primary outcome (stage 1)

The choice of 36 clusters provided 80% power to detect a 15% difference from an assumed 25% HIV testing plus linkage for male partners in the SOC arm, assuming a 0.1 value for the coefficient of variation (k).

6. Trial profile
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A trial profile figure based on the extension of the CONSORT for cluster randomised trials\(^1\) (annex-Figure 2) will be produced for each of the two trial stages illustrating the following:

i. Number of ANC days (clusters) in each randomisation group
   a. Total number of women and men across clusters
   b. Median number of women and men per clusters by trial arm
ii. Number of clusters lost to follow up
iii. Number of clusters and individuals analysed for each trial outcome, by arm

7. Baseline enrolment characteristics

Analyses will be done in R\(^2\) and Stata 14.0 (Stata Corp, Texas, USA). Baseline characteristics will be computed as proportions or median (interquartile range [IQR]), as appropriate, by arm in each of the two stages of the trial. We will examine baseline characteristics of men as reported by the woman (annex - Table 1 & 2), as well as baseline characteristics of women (annex - Table 3 & 4).

Individual level characteristics

- Age
- Literacy
- Highest level of education
- Occupation
- Marital status
- HIV testing history

8. Statistical analysis of primary outcome

We will assume that the two stages of the trial are independent\(^3\) and will proceed to carry out a test of the null hypothesis of no difference in effectiveness of each intervention compared to the SOC. We will do this by analysing data from the first stage first followed by interim decisions to drop arms; then we will conduct and analyse data from the second stage (no overlap of participants from the first stage).

The primary outcome analysis of the whole trial will thus combine p-values and estimates from the each separate stage\(^3\). The p-values from either stage will be combined using the weighted inverse normal (WIN) method\(^4\) for arms that are not dropped at interim. A weighted average of the log (risk ratio [RR]) will be computed for each intervention arm vs SOC, for the whole trial using estimates from each trial stage (Table 5). The estimates will be weighted using the inverse of the variance. All analyses will be by
intention-to-treat taking as the denominator the number of women who were eligible and take into account the clustered design.

In each cluster the proportion of male partners with the primary outcome will be calculated as:

\[
\frac{\text{number of male partners who have an HIV test + linked to male friendly clinic}}{\text{number of women recruited in that antenatal clinic day}}
\]

The distribution of these cluster-level estimates will be examined graphically by trial arm in each stage and a logarithm of the cluster-level summaries applied prior to further analysis if the distributions are right-skewed\(^5\). The geometric mean of clinic day proportions in each of the five intervention arms will be compared to the SOC arm using unpaired t-test \(^5\). An estimate of the RR and a 95% CI will also be computed for each comparison by dividing the geometric mean of proportions in each intervention arm and the geometric mean of proportions in the SOC arm\(^5\). Any variables that show imbalances will be adjusted for using a 2-stage analytical approach for both stages. First, a logistic regression model will be fitted to obtain a residual for each cluster; then these residuals will be analysed in place of the observed estimates.

This analysis involves more than two comparisons with a single control arm which can lead to higher than the specified family wise error rate (FWER) or significance level. Therefore, a Dunnett test \(^6\) will be applied to the t-statistics generated from the unpaired t-test to control the stage-wise FWER. Final decision-making at interim analysis will compare the Dunnett-corrected p-values to stage 1 FWER of 0.2. Since the two stages are assumed to be independent, cluster level summaries approach analogous to stage 1 analysis will also be followed in stage 2 comparing intervention arms that proceed to stage 2 with the SOC arm.

**Adaptations at interim analysis (end of stage 1)**

Interim analysis at the end of stage 1 will assess whether any of the five intervention arms should be dropped as recommended by an independent data monitoring and safety board (DSMB) based on a 3-part criteria. First, an arm whose statistical comparison to the SOC arm yields a p-value>0.2 will be considered for dropping for futility. Second, any intervention arm with high incidence of SAEs i.e. grade 3, 4 or 5 compared to SOC will be considered for dropping. It is the discretion of the DSMB to decide based on absolute number of SAEs in each intervention trial arm whether they are high or not. Such an
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observation and recommendation will then be shared with the investigators who will make the final decision. Thirdly, an arm may be maintained after taking into account the costs associated with providing the service in light of the p-value from statistical analysis. For this cost analysis, we will provide the DSMB estimates of the incremental cost per male partner tested, and incremental cost per male HIV positive identified through the intervention arms in comparison to the SOC arm. The investigators will access the first stage data only after the last follow-up visit for participants has occurred in order to perform interim analysis.

Descriptive analysis

We will explore intervention effects on the absolute number of male partners who started ART or got linked to VMMC by trial arm and trial stage (annex – Table 6). The components of the primary outcome will further be broken down into a) men who completed linkage i.e. started ART or got circumcised b) men whose linkage was incomplete: linked to ART or VMMC but did not start ART or were not circumcised.

We will explore if results differ by the self-reported HIV status of the woman; age of the man, recent HIV testing (<12 months); education level.

An estimate of the between-cluster variation, \( k \), will be provided for each stage.

9. Analysis of secondary outcomes

The four secondary outcomes are listed as follows:

i) Proportion of male partners who test for HIV within 28 days (as reported by the woman). This will be measured through audio computer assisted self-interview (ACASI) with the woman after her enrolment in the trial. The proportion and 95% Binomial Exact confidence interval (CI) of male partners reported to have had a test following the woman reenrolment will be computed using the number of women eligible at enrolment as the denominator.

ii) Proportion of women who accept to participate in their allocated trial arm. Measured by acceptance of the woman to continue participation in the allotted trial arm after knowing the activities in that particular arm. The proportion and 95% Binomial Exact CI of women who continue participation will be computed using the number of women eligible as the denominator, and shown by trial arm (Table 8).

iii) Risk of serious adverse events (SAEs) by males and females in the study; and the total cost of implementing each trial arm (see Section 10).

10. Safety analysis
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The total number of participants experiencing serious adverse events (SAEs) will be given as absolute numbers per arm. We expect these to be small hence no formal comparisons to the SOC will be made (annex- Table 7).

11. Sources of bias and contamination

Potential sources of bias which will be examined include:

- Contamination between clusters: it is possible for women or men from the SOC to benefit from the interventions such as by getting self-test kits. We will examine the proportion of participants in the SOC arm who report having received a self-test kit.
- We will check the fidelity of the phone call reminder by examining the proportion of participants who were successfully reached by the study staff
### Figure 1: Trial schema

| Trial arm                                      | 1st stage | 2nd stage | Phase III |
|-----------------------------------------------|-----------|-----------|-----------|
| 1. Standard of care                           |           |           | ? ≤ 3 arms|
| 2. Self-test kits (ST) only                   |           |           |           |
| 3. ST + Low amount incentive ($3)             |           |           |           |
| 4. ST + High amount incentive ($10)           |           |           |           |
| 5. ST + Low amount through lottery            |           |           |           |
| 6. ST + phone call reminder                   |           |           |           |

Total number of antenatal clinic days per arm
### Figure 2. Stage 1 & 2 trial profile

| Enrolment | Assessed for eligibility in stage 1 (n = 36 clusters) |
|-----------|------------------------------------------------------|
| Randomisation (n = 36 clusters) |

| Allocation |
|------------|
| Standard of care arm |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| Self-test kits only |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| ST + $3 incentive |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| ST + $10 incentive |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| ST + lottery incentive |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| ST + phone reminder |
| Total in ANC (n = ) |
| # women per ANC day (mean, range) |
| Total recruited (n = ) |
| Not recruited (n = ) |

| Analysis |
|----------|
| Total in ANC (n = ) |
| Not recruited (n = ) |
| # women per ANC day (mean, range) |

| Follow-up |
|----------|
| Total in ANC (n = ) |
| Lost to follow-up (n = 0 clusters) |

| Total recruited (n = ) |
| Not recruited (n = ) |

| # women per ANC day (mean, range) |

| Total recruited (n = ) |
| Not recruited (n = ) |

| # women per ANC day (mean, range) | Total recruited (n = ) |
| Not recruited (n = ) |

| # women per ANC day (mean, range) | Total recruited (n = ) |
| Not recruited (n = ) |

| # women per ANC day (mean, range) | Total recruited (n = ) |
| Not recruited (n = ) |

| # women per ANC day (mean, range) | Total recruited (n = ) |
| Not recruited (n = ) |
### Table 1 & 2: Stage 1 & 2 baseline characteristics of men as reported by the woman (N = XXXX)

| Variable               | Characteristic            | SOC | ST | ST + $3 | ST + $10 | ST + Lottery | ST + reminder |
|------------------------|---------------------------|-----|----|---------|----------|--------------|---------------|
| Number responded       | n                         |     |    |         |          |              |               |
| Age (years)            | Mean (sd)                 |     |    |         |          |              |               |
| Age group              | 18-19                     |     |    |         |          |              |               |
|                        | (20,30]                   |     |    |         |          |              |               |
|                        | (30,60]                   |     |    |         |          |              |               |
| Able to read and write | No                        |     |    |         |          |              |               |
| Education              | Never been to school      |     |    |         |          |              |               |
|                        | Primary                   |     |    |         |          |              |               |
|                        | Secondary                 |     |    |         |          |              |               |
|                        | Higher                    |     |    |         |          |              |               |
| Occupation             | Paid employee             |     |    |         |          |              |               |
|                        | Self-employed             |     |    |         |          |              |               |
|                        | Unemployed                |     |    |         |          |              |               |
| Ever tested for HIV    | No                        |     |    |         |          |              |               |
| Tested for HIV in the last 12m | No                   |     |    |         |          |              |               |
| Recruitment PHC        | Ndirande                  |     |    |         |          |              |               |
|                        | Bangwe                    |     |    |         |          |              |               |
|                        | Zingwangwa                |     |    |         |          |              |               |

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic
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**Table 3 & 4**: Stage 1 & 2 baseline characteristics of women (N = XXXX)

| Variable                  | Characteristic       | Trial arm       |
|---------------------------|----------------------|-----------------|
| Number responded          | n                    | SOC            |
| Age (years)               | Mean (sd)            | ST             |
| Age group                 | 18-19                | ST + $3        |
|                           | (20,30]              | ST + $10       |
|                           | (30,60]              | ST + Lottery   |
|                           |                      | ST + reminder  |
| Able to read and write    | No                   |                |
| Education                 | Never been to school |                |
|                           | Primary              |                |
|                           | Secondary            |                |
|                           | Higher               |                |
| Occupation                | Paid employee        |                |
|                           | Self-employed        |                |
|                           | Unemployed           |                |
| Ever tested for HIV       | No                   |                |
| Tested for HIV in the last 12m | No              |                |
| Recruitment PHC           | Ndirande             |                |
|                           | Bangwe              |                |
|                           | Zingwangwa         |                |

SOC: standard of care; ST: self-test kits; sd: standard deviation; MSCE: Malawi school certificate of education (4 years); PHC: primary health clinic
Table 5: Intervention effects by trial arm and trial stage

| Trial arm          | SOC | ST only | ST + $3 | ST + $10 | ST + Lottery† | ST + Reminder‡ |
|--------------------|-----|---------|---------|----------|---------------|---------------|
| **First stage**    |     |         |         |          |               |               |
| Eligible           |     |         |         |          |               |               |
| Outcome*           |     |         |         |          |               |               |
| Proportion**       |     |         |         |          |               |               |
| RR                 |     | 1       |         |          |               |               |
| 95% CI             |     |         |         |          |               |               |
| p-value            |     | NA      |         |          |               |               |
| **Second stage**   |     |         |         |          |               | Dropped       |
| Eligible           |     |         |         |          |               |               |
| Outcome*           |     |         |         |          |               |               |
| Proportion**       |     |         |         |          |               |               |
| RR                 |     |         |         |          |               |               |
| 95% CI             |     |         |         |          |               |               |
| p-value            |     |         |         |          |               |               |
| **First stage + second stage** |   |         |         |          |               |               |
| RR#                |     |         |         |          |               |               |
| 95% CI             |     |         |         |          |               |               |
| p-value§           |     |         |         |          |               |               |

SOC: standard of care; ST: self-test; RR: risk ratio
† 10% chance of winning $3 times number of men achieving the outcome
‡ phone call
* Evidence of testing and linked to clinic within 28 days regardless of test result
** Geometric mean of the cluster proportions
# Inverse variance weighted risk ratio
§ Using weighted inverse normal method
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**Table 6**: Starting HIV treatment or linkage to male circumcision by trial arm across the two stages

|                      | SOC   | ST only | ST + $3 | ST + $10 | ST + lottery | ST + reminder | Overall |
|----------------------|-------|---------|---------|----------|--------------|---------------|---------|
| n                    |       |         |         |          |              |               |         |
| %                    |       |         |         |          |              |               |         |

**Confirmatory testing**
- HIV positive
- HIV negative

**Total linked**

**Completed linkage**
- ART
- VMMC

**Linkage referred (incomplete)**
- ART
- VMMC

**No ART or VMMC indicated**
- HIV-ve already circumcised
  - HIV+ve already on ART

**Referred for ART or VMMC**

**Of total eligible**

SOC: standard of care; ST: self-test kits; VMMC: voluntary male medical circumcision
### Table 7: Adverse events and ACASI participation in women by trial arm and trial stage

| Trial arm | SOC | ST | ST+$3 | ST+$10 | ST+Lottery | ST+reminder | Total |
|-----------|-----|----|-------|--------|------------|-------------|-------|
| **First stage** | | | | | | | |
| Total number eligible for ACASI* | | | | | | | |
| Number interviewed at follow-up | | | | | | | |
| % of those eligible for ACASI | | | | | | | |
| Reported on an adverse event | | | | | | | |
| Through ACASI | | | | | | | |
| Direct report | | | | | | | |
| Through male friendly clinic | | | | | | | |
| **Second stage** | | | | | | | |
| Total number eligible for ACASI* | | | | | | | |
| Number interviewed at follow-up | | | | | | | |
| % of those eligible for ACASI | | | | | | | |
| Reported on an adverse event | | | | | | | |
| Through ACASI | | | | | | | |
| Direct report | | | | | | | |
| Through male friendly clinic | | | | | | | |

ACASI: audio computer-assisted self-interview; SOC: standard of care; ST: self-test kits

* Excluding **number of** women who discontinued after giving consent
### Table 8: Stage 1 & 2 women participation by trial arm stage

|                  | Total | SOC  | ST   | ST + $3 | ST + $10 | ST + Lottery | ST + reminder |
|------------------|-------|------|------|---------|----------|--------------|---------------|
| **Stage 1**      |       |      |      |         |          |              |               |
| Eligible         | 1084  | 198  | 187  | 146     | 216      | 155          | 182           |
| Consented        | 1084  | 198  | 187  | 146     | 216      | 155          | 182           |
| Discontinued     | 77    |      |      |         |          |              |               |
| by trial arm     | 7.1%  | 14 (7.1%) | 7 (3.7%) | 8 (5.5%) | 19 (8.8%) | 13 (8.4%) | 16 (8.8%)    |
| **Stage 2**      |       |      |      |         |          |              |               |
| Eligible         |       |      |      |         |          |              |               |
| Consented        |       |      |      |         |          |              |               |
| Discontinued     |       |      |      |         |          |              |               |
| by trial arm     |       |      |      |         |          |              |               |

SOC: standard of care; ST: self-test kits
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