21 May 2025

Statistical Analysis Plan – EDAM Cluster Randomised Trial

Section 1: Administrative Information

Title: Evaluation of an electronic clinical decision support algorithm to improve rural primary care management of acute febrile illness

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Version	Date	Changes made
0.1	11 June 2024	First draft prepared
0.2	2 October 2024, 17 October 2024	Enrolment targets updated according to latest strategy and projections; details added on DSMB monitoring; analysis plan updated; new references added.
0.3	10 January 2025	Made changes to sample size and statistical analysis sections. Also added a reference to the published protocol.
0.4	18 March 2025	Added in further relevant citation
0.5	8 May 2025	Dummy tables added Final changes to analysis methods made
1.0	19 May 2025	References formatted Comments resolved

Signatures:

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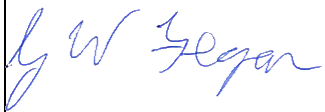
Signature			 CRChew (May 23, 2025 04:43 GMT+7)
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Section 2: Introduction

Background

Acute febrile illness (AFI) is a common reason for patient presentations to primary healthcare providers, such as primary healthcare centres (PHCs), in rural South and Southeast Asia. Malaria was previously a common cause of acute fever. However, the drastic reduction in malaria incidence due, in part, to the established use of malaria rapid diagnostic tests, means that presumptive treatment for malaria in such patients is no longer appropriate. Compounding this issue is that of poor clinical and laboratory diagnostic capacity because of low healthcare worker skills and the isolation of healthcare facilities. These factors lead to sub-optimal clinical decision-making, resulting in issues such as over-prescription of empirical antibiotic therapy and missed identification of patients needing higher-level care. In addition to the impact on the quality of patient care, over-prescription of antibiotics also drives antimicrobial resistance (AMR), a problem which is especially urgent in this region. Improving the management of acute fever by upskilling healthcare workers to treat more than just malaria also has the benefit of ensuring the success of malaria eradication programmes by maintaining confidence in primary healthcare services, as malaria treatment is dependent on patients continuing to seek care. In this study, rural primary health centres (PHCs) in Battambang province, Cambodia have been clustered together and then randomly assigned to different experimental groups to evaluate the impact of an electronic decision support tool on antibiotic prescribing for patients who present with acute fever**.**

Study hypothesis

Can an electronic clinical decision support tool which integrates clinical features, pulse oximetry, and malaria and C-reactive protein (CRP) rapid tests into an algorithm (the EDAM app) improve routine clinical management of patients with acute febrile illness?

Study design

Pragmatic cluster-randomized controlled trial with two study arms

Summary of study population (for more details, see Section 5)

Participant inclusion criteria

1. Age ≥1 year
2. Unscheduled presentation for acute care
3. Documented fever (≥37.5°C axillary) or hypothermia (<35.5°C) or history of fever in the last 24 hours

Target number of participants

2280 participants per arm (4,560 participants in total)

Participant exclusion criteria

1. Onset of illness >14 days
2. Presenting due to accident or trauma
3. Presenting ≤3 days after routine immunizations
4. Presenting within the follow-up period

Study duration

The enrolment period started in May 2024 and data collection is expected to be completed by mid-January 2025.

Outcomes

Primary outcome

Proportion of patients with acute fever aged ≥1 year who are prescribed antibiotics in the two study arms measured using data collected in the EDAM app by the end of the study

Secondary outcomes

The following secondary outcome measures use data collected in the EDAM app, except where measures are defined:

1. Proportion of patients with full recovery at 7 and 14 days in the two study arms
2. Proportion of patients referred to hospital at presentation in the two study arms
3. Proportion of patients in the intervention arm whose management followed the EDAM recommendations
4. Proportion of patients with unplanned re-presentations at 7 and 14 days (if not fully recovered by 7 days) in the two study arms; for patients who re-present, proportion prescribed antibiotics
5. Proportion of patients with severe clinical outcomes (death or hospitalization) at 7 and 14 days (if not fully recovered by 7 days) in the two study arms, not including those referred to hospital at presentation.
6. Proportion of patients prescribed an antibiotic in the intervention arm with:
    - 6.1. CRP less than 10 mg/L
    - 6.2. CRP more than or equal to 10mg/L, less than or equal to 80mg/L
    - 6.3. CRP more than 80mg/L
7. Measure of usability and acceptability measured using structured interviews conducted with the healthcare workers in the intervention arm at the end of the study to determine whether EDAM is usable and useful and whether they support its continued use (a separate ethical approval application will be made for this work).
8. Measure of cost-effectiveness measured using study records by the end of the study: A cost-effectiveness analysis will be carried out to assess the budget implications of introducing EDAM.

Purpose and scope of this document

This Statistical Analysis Plan (SAP) presents the proposed statistical principles and analysis methods for the evaluation of the EDAM trial. The structure of this document is partially based on Gamble et. al.'s checklist[1] and the draft guidance currently being developed by Karla Hemming *et al* for CRT SAPs (personal correspondence). Hemming and colleagues are in the process of developing guidelines akin to Gambles for CRTs[2].

Section 3: Study Methods

Trial design: Summary

- Study type: Pragmatic, cluster-randomised controlled trial
- Number of study arms: 2 (intervention; control)
- Number of clusters: 15 in each arm (30 in total)
- Clusters: Primary healthcare centre (PHC)
- Population: Patients aged 1 year and older presenting to primary health centres with acute febrile illness (AFI) in three operational districts (OD) in Battambang, Cambodia
- Sample size: Average of 150 individual participants per cluster (2,280 participants in each arm)
- Intervention: Electronic clinical decision support algorithm (eCDSA) encompassing pulse oximetry and point-of-care C-reactive protein (CRP) testing, and associated training
- Comparison/Control: Normal standard of care for AFI management in primary care

Randomisation

Pseudo-randomisation was performed using the *ralloc* package in Stata, stratified by OD to ensure an equal distribution of intervention and control PHCs within each OD. The pseudo-randomisation list (A or B) was merged 1:1 with the list of PHCs. Allocation of A and B to the intervention or control arm was performed using the flip of a coin.

Further details are available at: Randomisation methods EDAM Study.docx and in *Appendix 1*.

Sample size

Please refer to section 6.2 in the published Study Protocol[3] for full details. Briefly, with 15 clusters per arm the target number of participants to be enrolled on average per cluster is 152 assuming a drop-out rate of 10%. In total, the target number of patients to be recruited is therefore 4560. These calculations were based on hypothesised values of the primary outcome (percentage of study participants being prescribed antibiotics) of 17.5% and 25% for the intervention and control arms respectively and with a 0.05 probability of Type I and 0.2 probability of Type 2 error plus an assumed intra-class correlation coefficient of 0.025[1][2]). The hypothesised values of the primary outcome were derived from

a) the findings of a large epidemiological study in rural South and Southeast Asia which showed that approximately 25% of patients seen in primary health centres for acute febrile illness were prescribed antibiotics and that upper respiratory tract infection was the predominant clinical syndrome (data being prepared for publication). Upper respiratory tract infection is almost always viral and does not require antibiotic treatment.
b) the findings of a multicentre open-label randomised controlled trial in Vietnam which showed that CRP testing reduced antibiotic prescription in patients with upper respiratory tract infection[6].

Framework

We adopted a superiority hypothesis in that we hypothesize that the intervention will result in a statistically significant reduction in the proportion of patients with AFI who are prescribed

antibiotics in a PHC setting – assuming an equivalence in safety outcomes (see Section 6: Analysis – Outcome definitions) between both arms.

Statistical interim analyses and stopping guidance

Given that the intervention poses a low risk to the patient, no formal interim analyses are planned. However, the independent Data Safety Monitoring Board (DSMB) will review study outcomes via the real-time dashboard at periodic intervals (approximately every 1,500 enrolled participants) . This will not affect the chosen significance level for the primary outcome. DSMB reviews will focus primarily on identifying selection bias, as advised by Hemming et. al.[2], given that the trial is unblinded.

Timing of final analysis

We expect all analyses to be completed within 6 months from when the trial database is locked, i.e. when follow-up has been completed for all enrolled participants and the data have been cleaned.

Timing of outcome assessments

Safety outcomes will be assessed 7 days after enrolment and, for individuals who do not report full recovery from their illness at day 7, at 14 days. A window period of +2 days will be allowed.

Section 4: Statistical Principles

Confidence intervals and p-values

We will report 95% confidence intervals around all quantitative outcome measures. As standard, a P value of <0.05 will be considered statistically significant.

Steps will be taken to ensure that consecutive screening occurs of patients presenting acutely to PHCs, with the EDAM algorithm consequently supporting the objective, structured assessment for eligibility of the patient.

Adherence and protocol deviations

Adherence to the intervention is ensured by provision of the relevant version of the EDAM algorithm to the healthcare workers operating at the PHCs in each arm; thus, only healthcare workers working in PHCs allocated to the intervention arm will have access to the recommendations and guidance of the eCDSA. Importantly, however, the eCDSA is designed to only provide guidance rather than be prescriptive. As such, the extent of agreement between the recommended advice and the healthcare worker's chosen management plan (as defined by two outcomes: i) antibiotic prescription and ii) referral to hospital) will be measured and reported.

Examples of significant protocol deviations may include:

- Ineligibility i.e., enrolling a patient who did not meet the criteria for enrolment
- Enrolling a patient into the wrong study arm, by using the wrong version of the EDAM app
- Follow-up phone call missed within the defined windows (+2 days)
- Patients enrolled more than once in the trial whilst still in active follow-up.

The investigators may choose to discontinue a participant from the study in the case of a significant protocol deviation. The reason for withdrawal will be recorded in the participant's study file.

Analysis populations

The primary outcome will be assessed in the intention-to-treat (ITT) population.

A per-protocol analysis will be performed among participants who are not involved in a significant protocol deviation, as outlined above, *and* – for analyses on outcomes recorded during follow-up – who do not withdraw or withhold consent for follow-up.

All analyses are expected to be complete case analyses for the outcomes of interest, given that the electronic data collection tool did not allow progression through and completion of the form without entering all essential data.

Section 5: Trial Population

Screening data

All patients presenting to the PHCs as an unscheduled presentation (i.e., without an appointment) will be screened for eligibility.

Eligibility

The inclusion and exclusion criteria for the study are as follows.

Inclusion criteria

- Age ≥ 1 year
- Unscheduled presentation for acute care
- Documented fever (≥ 37.5°C axillary) or hypothermia (< 35.5°C) or history of fever in the last 24 hours

Exclusion criteria

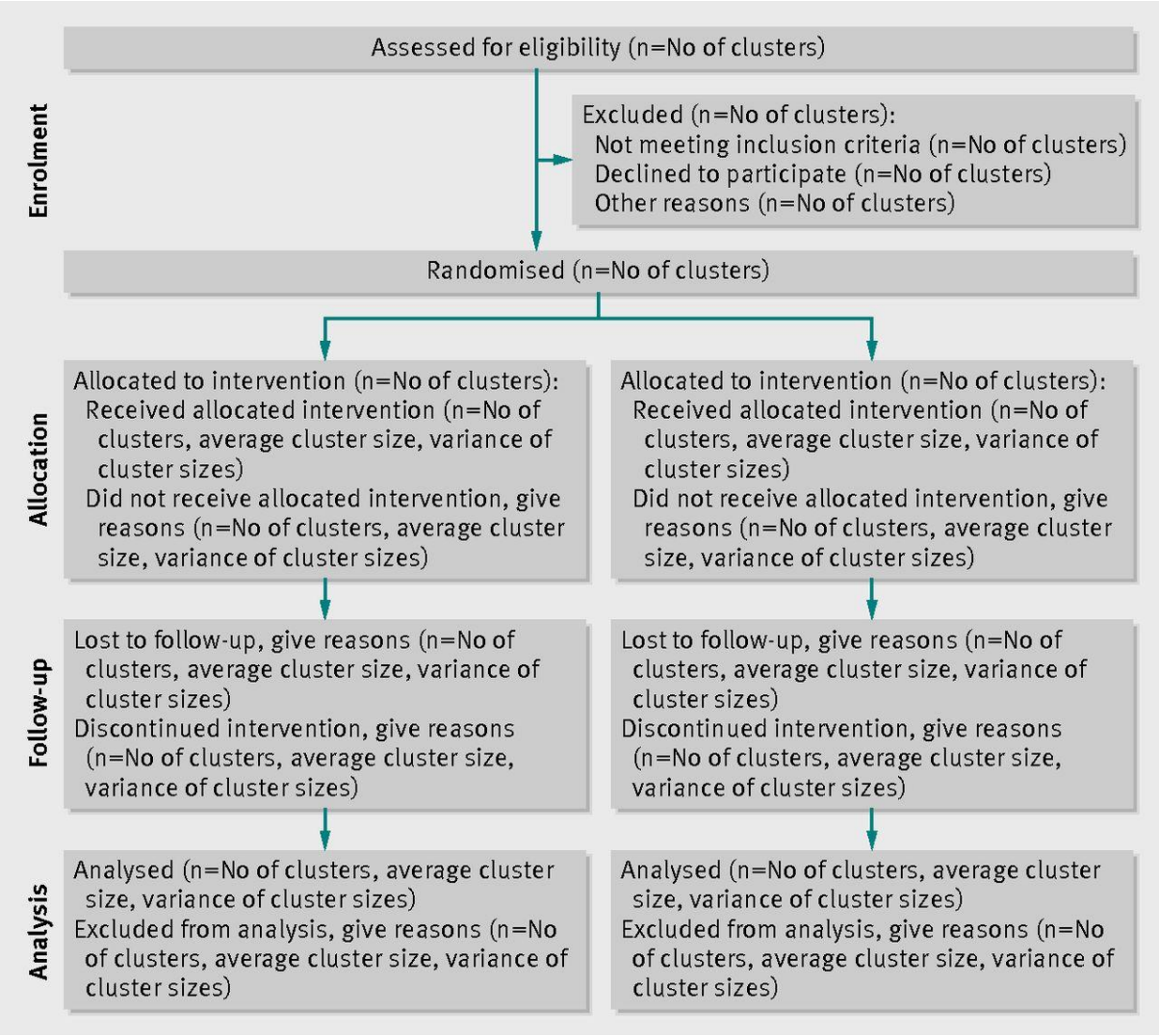
- Onset of illness > 14 days
- Presenting due to accident or trauma
- Presenting ≤ 3 days after routine immunizations
- Presenting within the follow-up period

Should a patient not meet all criteria, enrolment will not be permitted by the internal logic of the EDAM app, which will also be used for data collection. The app will advise healthcare workers in intervention arm PHCs to continue standard practice for non-eligible patients.

Recruitment

A CONSORT flow diagram as shown in Figure 1 below will be produced.

Figure 1. Flow diagram template to show the progress of clusters and individual patients through phases of the cluster-randomised trial[7]



Withdrawal/follow-up

Participants may withdraw their consent for follow-up at any time. The number and proportion of patients who do not consent to follow-up in each arm will be reported. Loss to follow-up will be defined as a participant who did not otherwise withdraw consent for follow-up but who is uncontactable despite three attempts to establish contact *and* attempt to locate the patient using a village health worker (VHW). If the VHW is able to locate the participant, a suitable telephone number to contact the patient will be recorded or the study team may choose to visit the participant at home.

As the trial does not require written informed consent, participants cannot withdraw consent to undergo clinical management according to the intervention.

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Baseline patient characteristics

Baseline characteristics of the individual participants in the study population will be presented between intervention and control arms (see planned Table 1 below). Data to be reported will include: age (in years, and grouped: 1-4, 5-14, 15+ years), sex (female, male, other), fever status at enrolment (temperature at enrolment: <37.5 [i.e., fever in the past 24 hours but not at presentation], >= 37.5), operational district (OD Moung Russey, OD Thmarkoul, OD Battambang), age-specific observed or measured danger signs present at presentation (yes/no), and presenting symptom(s) at enrolment, by organ system (respiratory and ear, nose, throat; gastro-intestinal; urinary; skin and soft tissue; musculoskeletal).

Continuous variables will be reported as mean (SD, 95% confidence interval [CI] of mean) and binary or categorical variables as n/N (%).

Table 1. Planned Table 1: Baseline characteristics of study population, by trial arm

	Intervention arm (N=)	Control arm (N=)
Age, years (mean, SD, 95% CI)		
Age group (n, %)		
1-4		
5-14		
15+		
Sex (n, %)		
Female		
Male		
Other		
Temperature at enrolment, degrees Celsius (n, %)		
<37.5 (i.e., fever in past 24 hours)		
>= 37.5		
Operational District (n, %)		
Battambang		
Moung Russey		
Thmarkoul		
Danger signs present at enrolment (n, %)		
Present		
Not present		
Symptoms present at enrolment, by organ system (n, %)		
Upper respiratory tract		

Lower respiratory tract		
Other ear, nose and throat (ENT)		
Gastro-intestinal		
Skin and soft tissue		
Musculoskeletal		
Urinary tract		

Section 6: Analysis

Outcome definitions

Table 2 below provides an overview of the key primary outcome and secondary outcomes to be analysed.

Table 2. Overview of primary and secondary outcomes with corresponding population for analysis, comparison groups and residual confounders to be adjusted for.

	Outcome measure	Population	Comparison	Confounders
Primary outcome	Proportion (n/N, %) of study participants prescribed antibiotics	All participants	Intervention and control arms	Age group Sex
Secondary outcomes	Proportion (n/N, %) of study participants with full recovery at 7 and 14 days after enrolment	All participants	Intervention and control arms	Age group Sex
	Proportion (n/N, %) of study participants referred to hospital at presentation	All participants	Intervention and control arms	Age group Sex
	Proportion (n/N, %) of participants in the intervention arm whose management followed the EDAM recommendations	Participants in intervention arm	Age group	Sex
	Proportion (n/N, %) of study participants with unplanned re-presentations to any health facility at 7 and 14 days	All participants	Intervention and control arms	Age group Sex
	Among participants who re-represented to a healthcare facility, the proportion (n/N, %) of study participants who obtained antibiotics, either via prescription or via independent purchase	Participants who re-presented to a healthcare facility	Intervention and control arms	Age group Sex
	Proportion (n/N, %) of study participants with severe outcomes (hospitalisation or death) at day 7 and day 14	Excluding participants referred to hospital at presentation	Intervention and control arms	Age group Sex
	Proportion of patients prescribed an antibiotic in the intervention arm	Participants in intervention arm	CRP level (<10 mg/L, 10-80 mg/L, >80 mg/L)	Age group Sex

In addition, several descriptive outcomes related to acceptability of the algorithm among the healthcare workers taking part in the trial will be reported within the intervention arm only (*Table 3)* and coupled with additional qualitative research not defined in this SAP.

Table 3. Overview of acceptability outcomes to be reported among healthcare workers assigned to the intervention arm

Outcome measure	**Sub-group analyses**
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for positive antibiotic prescription (i.e. agreed to prescribe antibiotics)	Age group CRP level
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for negative antibiotic prescription (i.e. agreed *not* to prescribe antibiotics)	Age group CRP level
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for positive hospital referral (i.e., agreed to refer to hospital)	Age group CRP level
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for negative hospital referral (i.e., agreed *not* to refer to hospital)	Age group CRP level

Analysis methods

For all outcomes listed in *Table 2* above, generalised linear mixed models (GLMM) with a binomial distribution and logit link will be used. The GLMM will include PHCs as a random effect to account for clustering at PHC level, and treatment group and potential residual confounding factors (e.g. age group, sex) as fixed effects. GLMM have been shown to have greater power than cluster-level analysis for studies with 20-30 clusters with varying cluster size[8]. The effect measures between treatment groups (intervention and control) will be reported as adjusted odds ratios (aORs) between treatment arms, with corresponding 95% confidence intervals (CI). Risk ratios and risk differences (to ensure both relative and absolute measures are reported, as recommended by the Consolidated Standards of Reporting Trials [CONSORT] statement) will also be calculated. A binomial regression approach will be used, however, should model convergence problems occur the relative risks (RR) will be calculated using the method proposed by Zou.[9]

The observed intra-cluster correlation coefficient (ICC) for the primary outcome will be calculated.

Table 4. Planned table of results of primary outcome: Proportions of participants prescribed antibiotics in intervention and control arms, with corresponding relative and absolute outcome measures

	Intervention group (n/N, %)	Control group (n/N, %)	Adjusted odds ratio (aOR) (95% confidence intervals [CIs])	Adjusted risk ratio (aRR) (95% CIs)	Adjusted risk difference (aRD) (95% CIs)
Overall					
Age group, years					
1-4					
5-14					
15+					
Sex					
Female					
Male					

Table 5. Planned table of results of secondary outcomes: Proportions of participants with each outcome in intervention and control arms, with corresponding relative and absolute outcome measures

Secondary outcome	Intervention arm (n/N, %)	Control arm (n/N, %)	Adjusted odds ratio (aOR, 95% CI)*	Adjusted relative risk (aRR, 95% CI)*	Adjusted risk difference (aRR, 95% CI)*
Proportion (n/N, %) of study participants with full recovery at 7 and 14 days after enrolment					
Proportion (n/N, %) of study participants referred to hospital at presentation					
Proportion (n/N, %) of study participants with unplanned re-presentations to any health facility at 7 and 14 days					
Among participants who re-presented to a healthcare facility, the proportion (n/N, %) of study participants who obtained antibiotics, either via prescription or via independent purchase					
Proportion (n/N, %) of study participants with severe outcomes (hospitalisation or death) at day 7 and day 14					

* Adjusted for: participant age group and sex

Table 6. Planned table of descriptive secondary outcomes in intervention arm only, overall and stratified by CRP result and age group

		By CRP level, mg/L			By age group, years		
	Overall	<10	10-80	>80	1-4	5-14	15+
N							
Proportion (n/N, %) of participants in the intervention arm whose management followed the EDAM recommendations							
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for positive antibiotic prescription (i.e. agreed to prescribe antibiotics)							
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for negative antibiotic prescription (i.e. agreed *not* to prescribe antibiotics)							
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for positive hospital referral (i.e., agreed to refer to hospital)							
Proportion (n/N, %) of study participants for whom the healthcare worker complied with the recommended management for negative hospital referral (i.e., agreed *not* to refer to hospital)							

Missing data

Due to in-built data quality control measures within the EDAM app, progression through the algorithm requires all essential data to be completed. As such, we do not expect missing data on the primary outcome. Missing data may be present in the secondary outcomes if the patient is lost to follow-up or declined/withdrew follow-up. Baseline characteristics of participants who did and did not complete the day 7 follow-up form will be compared to assess the randomness of the missing data. Missing data will not be imputed.

Harms

Reporting on patient outcomes (including recovery from illness and severe outcomes including hospitalisation and death) is described above. The results of any investigation of safety concerns by the DSMB will be reported.

Statistical software

All data analyses will be performed in Stata, version 18.0.

References

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Appendix

1. Randomisation methods EDAM Cluster Randomised Trial

The following brief document outlines the approach taken for randomisation and allocation of clusters within the EDAM Trial, to provide a record of the steps taken to be used in later publications. It is for internal MORU use only.

Brief study overview:

- Study type: Cluster-randomised clinical trial
- Population: Patients aged 1 year and older presenting to primary health centres with acute febrile illness (AFI) in three districts in Battambang, Cambodia
- Intervention: Electronic clinical decision support algorithm (eCDSA) encompassing pulse oximetry and point-of-care C-reactive protein (CRP) testing
- Comparison: Normal standard of care for AFI management in primary care
- Primary outcome: Proportion of patients with AFI who are prescribed any antibiotics

Method of randomisation:

1. Stratified per Operational District (10 clusters per district)
2. Pseudo-randomisation list of allocation to 1 of 2 possible arms (A or B) generated using the *ralloc* package in Stata (Stata .do list saved as: "...../gen_randlist_edam.do")
3. Randomisation list merged 1:1 with list of primary healthcare centres (PHC)
4. Allocation of A or B to Intervention or Control performed using the flip of a coin, where heads= A is intervention and tails= B is intervention

Outcome of flip of coin for arm allocation:

Tails, therefore B represents the intervention arm and A represents the control arm.

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Final Audit Report 2025-05-22

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