# Supplemental Information S1: Appendix

## S1.1 EDAM Clinical Trial Overview

Computerised clinical decision support systems (CDSS) are a category of digital health technologies designed to assist healthcare providers in clinical decision-making, including in the context of antimicrobial stewardship. The Electronic Clinical Decision Support for Acute Fever Management (EDAM) app is one such tool, developed to guide the clinical management of patients presenting with acute febrile illness (AFI) in primary health care settings.

A cluster-randomised controlled trial was conducted to evaluate the effectiveness of the EDAM tool in Battambang Province, Cambodia. 30 primary health centres (PHCs) participated in the trial, of which 15 were randomly assigned to implement the intervention. The trial was completed in early 2025.

EDAM is an Android tablet–based application designed to support clinical management pathways for AFI patients. Unlike standard practice, where malaria rapid diagnostic tests (RDTs) are administered at the beginning of the patient consultation, the EDAM tool follows a structured clinical algorithm. This algorithm combines measured vital signs and a symptoms assessment with the use of malaria RDTs and C-reactive protein (CRP) testing to guide clinical decision-making. The aim of the tool is to support improved diagnostic accuracy, promote the appropriate use of antibiotics, and encourage timely referral for higher-level care when warranted.

The study population included patients aged over one year, presenting to a PHC with a documented fever during an unscheduled visit. Patients were excluded if they had experienced a fever for more than 14 days, presented due to an accident or trauma, or had recently had routine immunisation.

## S1.2 Model Overview

The decision tree model consists of two main branches representing the comparator and intervention arms of the clinical trial. All patients begin at the root node, “Trial Randomisation”, at the point of presentation to a PHC. Patients have the same likelihood of entering each arm.

In the control arm (lower branch of Figure 2.1 in the main report), patients first receive a malaria RDT, as standard of care. Possible outcomes from the malaria RDT node are malaria-positive, malaria-negative, or no malaria RDT (refusal of the test). Regardless of malaria RDT results, the PHC worker may choose to prescribe antibiotics or not, including for malaria-positive cases where co-infections or multiple diagnoses may be present. After the antibiotic prescribing nodes, each clinical pathway terminates in one of two health outcomes, measured at seven days post-initial presentation: treatment success (fever resolved) by follow-up or treatment failure (fever not resolved).

The intervention arm (upper branch of Figure 2.1 in the main report) introduces an expanded clinical assessment that incorporates the EDAM intervention. All patients are first evaluated for danger signs based on observed and measured vital signs, which include mental status, ability to eat and walk, heart rate, respiratory rate, blood pressure, and oxygen saturation. Patients who exhibit one or more danger sign(s) are classified as having potential severe illness and are routed to the lower severe illness sub-branch. These individuals receive a malaria RDT and follow the same clinical decision and treatment pathway as patients in the control arm.

Patients without danger signs proceed to a symptom-based assessment, covering respiratory, gastrointestinal, and other symptom categories. Following this assessment, all patients receive a malaria RDT. Patients are then filtered into either an ‘upper respiratory symptoms (URS) present’ or ‘no upper respiratory symptoms (URS) present’ node. Those with respiratory symptoms are additionally tested using a C-reactive protein (CRP) test. Based on these diagnostic inputs, patients in both the URS and no URS nodes receive a final clinical assessment and are either prescribed antibiotics or not, before progressing to the terminal outcomes of treatment success or failure in follow-up.

Probabilities assigned to each branch are informed by empirical data derived from the clinical trial.

A custom R function, ‘CalculateExpectedValues’, was developed to recursively calculate the expected costs and disability-adjusted life years (DALYs) for each node of the decision tree model.

For terminal nodes, the function directly assigns the values for cost and DALYs to the node’s expected cost and expected health attributes.

For internal nodes, the function iterates over all ‘child’ nodes, to ensure that the expected values for all descendant nodes have been calculated. It then multiplies each child’s expected cost and DALYs by the probability of reaching that child node (p), summing across all children nodes to compute the weighted averages. These weighted averages represent the expected cost and expected DALYs for the current (parent) decision node.

This approach ensures that expected values are propagated from the terminal nodes upward through the decision tree (‘folding up’), allowing for accurate estimation of overall expected costs and DALYs for both arms.

A mixed-effects logistic regression model was fitted to the trial data using the glmer() function from the lme4 package in R. The binary primary outcome was modelled with fixed effects for trial arm, age group, and sex, and a random intercept for PHC to account for clustering. Variance components for the random effects were extracted using the VarCorr() function and converted to a data frame. The between-cluster variance, given by the variance of the random intercept for PHC (var\_comp$vcov[1]), was used to calculate the intra-cluster correlation coefficient (ICC). This value represents the proportion of total variance in the outcome attributable to differences between PHCs.

## S1.3 Model Assumptions

A key assumption made within the cost-effectiveness analysis is the inclusion of antimicrobial resistance (AMR) costs. This analysis cites a 2018 study enumerating the costs of antimicrobial resistance per antibiotic consumed for eight classes of antibiotic(1). For the purposes of this economic analysis, all antibiotics prescribed in the EDAM clinical trial were classified as either a narrow spectrum penicillin (NSP) or quinolone. Assumptions for such classification is as follows:

1. Metronidazole is active against only anaerobic bacteria, and is therefore given the AMR cost of a narrow spectrum antibiotic.
2. Cotrimoxazole is a combination of a sulphonamide and a dihydrofolate reductase inhibitor. Its AMR cost was extrapolated from that of quinolones due to its relatively similar spectrum.

For societal costs and productivity loss calculations, the model assumes 3.5 days of work lost for patients who have recovered from acute fever by the follow-up period. Patients who have not recovered have an assumed seven days of work lost.

## S1.4 Equations

### Equation 1.4.1 Cambodia’s Cost-Effectiveness Threshold(2)

### Equation 1.4.2 Antibiotic Costs

Cost in KHR for each antibiotic was sourced from Mahidol-Oxford Tropical Medicine Research Unit (MORU) procurement receipts. Course duration information was extracted from the World Health Organisation (WHO) Access, Watch, Reserve report.(4)

### Equation 1.4.3 Antimicrobial Resistance Costs(1)

The cost value in each equation was obtained from the Shrestha et al., 2018 report on enumerating the cost of antimicrobial resistance, provided in 2018 Thai Baht (1).

### Equation 1.4.4 Terminal Node Costs from the Societal Perspective

Control Arm Terminal Nodes’ Costs

Intervention Arm Terminal Nodes’ Costs

*Costs Key:*

RDT: cost of malaria rapid diagnostic test,

Apptcontrol: cost of primary health centre appointment in control arm,

ApptIntervention: cost of primary health centre appointment in intervention arm,

FollowUp: cost of primary health centre appointment,

EDAM: cost of one use of the EDAM intervention,

Bloodpressure: cost of one use of the blood pressure machine,

Pulseox: cost of one use of the pulse oximeter,

CRP: cost of C-Reactive Protein test

Hospitaladmission: cost of Cambodia’s inpatient bed-day,

RepresentPHC: cost of primary health centre appointment,

ABWeightedCosts: average cost of antibiotic course prescribed [in given node],

AMRWeightedCosts: average cost of antimicrobial resistance per antibiotic consumption [in given node],

Productivitysuccess: cost of productivity loss for 3.5 days sick,

Productivityfailure: cost of productivity loss for 7 days sick

*Probabilities Key:*

pHospitalRef: probability of hospital referral within initial appointment [in given node],

pFollowUpHospAdmit: probability of hospital admission during 7-day follow-up period [in given node],

pRepresent: probability of an unscheduled representation to a primary health centre during 7-day follow-up period [in given node]

\*Only applied to terminal nodes where malaria RDT was not refused.

\*\*Only applied to terminal nodes that represent treatment failure at follow-up.

\*\*\*Only applied to terminal nodes where antibiotic prescribing occurred.

Only applied to terminal nodes where upper respiratory symptoms were present.

### Equation 1.4.5 Clustering Effect Equations

## S1.5 Figures

### A graph with lines in it AI-generated content may be incorrect.Figure 1.5.1 Base Case Comparison of EDAM Intervention and Control in Terms of Cost and Antibiotic Treated Patients Averted

EDAM: electronic clinical decision support for acute fever management, USD: U.S dollar

### A graph of numbers and lines AI-generated content may be incorrect.Figure 1.5.2 Probabilistic Sensitivity Analysis: Incremental Cost vs. DALYs Averted

DALYs: disability-adjusted life years, USD: U.S dollar

### Figure 1.5.3 Probabilistic Sensitivity Analysis: Distribution of Antibiotic Treated Patients Averted

A graph of a number of patients

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### A graph of a graph AI-generated content may be incorrect.Figure 1.5.4 Probabilistic Sensitivity Analysis: Distribution of Intervention Costs

EDAM: electronic clinical decision support for acute fever management, USD: U.S dollar

### Figure 1.5.5 Probabilistic Sensitivity Analysis: Distribution of Net Monetary Benefit

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EDAM: electronic clinical decision support for acute fever management

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CRP: C-Reactive Protein Test, EDAM: electronic clinical decision support for acute fever management, RDT: rapid diagnostic test

### Figure 1.5.7 Determinants of Net Monetary Benefit Variation: Absolute Regression Coefficients of Antibiotic Cost Inputs

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AB: antibiotic, RDT: rapid diagnostic test, URS: upper respiratory symptoms

### A graph with a bar graph AI-generated content may be incorrect.Figure 1.5.8 Determinants of Net Monetary Benefit Variation: Absolute Regression Coefficients of Antimicrobial Resistance Cost Inputs

AMR: antimicrobial resistance, RDT: rapid diagnostic test, URS: upper respiratory symptoms

### Figure 1.5.9 Comparison of Base Case and Scenario Analysis ICERs Across Two Effectiveness Metrics

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DALYs: disability-adjusted life years, ICER: incremental cost-effectiveness ratio, USD: U.S dollar

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RDT: rapid diagnostic test, UR: upper respiratory

## S1.6 References

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