Study title:	**Evaluation of an electronic clinical decision support algorithm to improve rural primary care management of acute febrile illness**	
Short title:	Electronic clinical Decision support for Acute fever Management (EDAM)	
Study design:	Implementation study using a cluster-randomised controlled trial design	
Study site:	Battambang province, Cambodia	
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Conflict of interest statement

The Principal Investigator and investigators declare they have no conflict of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the authorised individuals from the University of Oxford, the Investigator Team and members of the Oxford Tropical Research Ethics Committee (OxTREC) and local Ethics committee, unless authorised to do so.

Rusheng Chew		13 February 2024
Principal Investigator	Signature	Date

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SYNOPSIS

Study title	Evaluation of an electronic clinical decision support algorithm to improve rural primary care management of acute febrile illness
Short title (Acronym):	Electronic clinical Decision support for Acute fever Management (EDAM)
Protocol no.	HCR23008
OxTREC Reference No.:	550-23
Clinical Trial registration No.:	ISRCTN15157105
Study design:	Implementation study using a cluster-randomised controlled trial design
Study site:	Primary health centres (PHCs) in Battambang province, Cambodia
Intervention	The intervention is the use of the EDAM app. PHCs will be randomly allocated into two study arms using a computer-generated procedure; • Arm 1: EDAM-guided clinical management arm (N = 15 PHCs) • Arm 2: control (standard care) arm (N = 15 PHCs)
Study patient	This study will be conducted in patients with acute febrile illness (AFI) presenting to primary health centres (PHCs) in the study site.
Planned study period	Total duration of the trial is 9-12 months (6-9 months for data collection and 3 months for analysis).

ABBREVIATIONS

AFI	Acute febrile illness
AHEAD	Action for Health Development
AMR	Antimicrobial resistance
AVPU	Alert, Responds to Verbal stimulus, Responds to Painful stimulus, Unresponsive
CI	Confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CNM	National Center for Parasitology, Entomology and Malaria Control, Cambodia
COMRU	Cambodia Oxford Medical Research Unit
CRP	C-reactive protein
DSMB	Data and Safety Monitoring Board
eCDSA	Electronic clinical decision support algorithm
EDAM	Electronic clinical Decision support for Acute fever Management
LMIC	Low-and middle-income country/ies
mg/L	Milligram per litre
mmHg	Millimetre of mercury
MORU	Mahidol Oxford Tropical Medicine Research Unit
NGO	Non-governmental organization
OxTREC	Oxford Tropical Research Ethics Committee
PHCs	Primary health centres
SAP	Statistical Analysis Plan
SEACTN	South and Southeast Asian Community-based Trials Network
SpO_2	Peripheral arterial oxygen saturation
WHO	World Health Organization

1. BACKGROUND AND RATIONALE

1.1 Background

Acute febrile illness (AFI) is a common reason for patient presentations to primary healthcare providers, such as primary health-care centres (PHCs), in rural South and Southeast Asia.[1] Malaria was previously a common cause for 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 skillsets and 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 health-care services, as malaria treatment is dependent on patients continuing to seek care.

Previous work in South and Southeast Asian low- and middle-income countries (LMICs), and LMICs elsewhere, have assessed the efficacy and/or cost-effectiveness of simple tools to aid clinical decision-making for AFI, such as pulse oximetry and C-reactive protein (CRP) rapid tests.[2-5] The use of algorithms based on clinical symptoms and signs, such as the World Health Organization (WHO) Integrated Management of Childhood Illness, is also well-established. However, these algorithms are paper-based and only relevant to children <5 years old. Electronic clinical decision support algorithms (eCDSAs) integrating point-of-care diagnostics, pulse oximetry, and symptom-based algorithms and accessed on mobile devices may be a more efficient and user-friendly way of deploying such clinical decision support assistance to rural PHCs, with encouraging results from one study in sub-Saharan Africa.[6] However, to date no such eCDSA tailored to rural South and Southeast Asian primary care settings has been developed or assessed under real-world conditions.

Since 2021, we have been running a large-scale observational study aiming to define the regional epidemiology of AFI in primary care through the South and Southeast Asian Community-based Trials Network (SEACTN).[7] This study, called SEACTN Rural Febrile Illness (RFI) Project Work Package A (Study title “Determining the incidence, causes and outcomes of rural febrile illness (RFI) in South and Southeast Asia, as part of the South and Southeast Asian Community-based Trials Network (SEACTN). Work Package A (WP-A)”, OxTREC Ref.: 543-20, Protocol No.: BAC20001), has sites in five countries (Thailand, Bangladesh, Laos, Cambodia, and Myanmar) and a target recruitment number of 100000 patients, of which over 75000 have been recruited as of June 2023. Patient enrolment is performed by health workers in PHCs, along with village health workers. As part of this study, we have collected detailed data on clinical symptoms and vital signs, which have allowed formulation of age-appropriate syndromic diagnoses using algorithms developed by a committee of experts comprising an adult infectious diseases and respiratory physician (RC), an adult general and infectious diseases physician (ND), an adult general physician (AC), a paediatric infectious disease specialist (Prof Enitan Carrol, Liverpool School of Tropical Medicine), and a general practitioner (JC), all of whom have extensive experience working in developing world settings.

We have integrated these syndromic decision rules, malaria and CRP rapid tests, pulse oximetry, and local management guidelines (where these exist) to create an eCDSA called EDAM (Electronic clinical Decision support for Acute fever Management) for the diagnosis and management of acute fever in

South and Southeast Asia. Importantly, EDAM's integrated recommendations for clinical management will be reviewed and ratified through consultation with local clinicians to ensure they follow national guidelines and are customized to the local context. EDAM will take the form of an app which can be deployed on mobile devices such as tablets and smartphones, with the capability to function without an Internet connection. This effort has been motivated by the appetite among experts, policymakers, and healthcare workers in PHCs for algorithmic management of AFI incorporating point-of-care tests which have the potential to change management, as documented in a series of stakeholder analyses we conducted across SEACTN countries (Liverani et al., manuscript in preparation) and as described in the literature.[8 9]

Of note, CRP rapid tests and pulse oximetry are currently not routinely used as part of the primary care management of AFI in the settings where this trial is to be run. Additionally, as the sites are heterogenous, the recommended management for each syndromic diagnosis has been developed using existing guidelines where they exist, as well as the input of senior clinicians at each site. The development and evaluation of the EDAM prototype to be used in this study has been guided by consultation and engagement with local health authorities to ensure inclusivity and setting-specific appropriateness. The results of this consultation will be published to serve as a guide for others wishing to develop similar eCDSAs. Evidence from similar eCDSAs used in other LMIC settings, such as ePOCT and inSCALE in sub-Saharan Africa,[6 10] has also been taken into consideration. In addition, as part of this study, an assessment of the usability and acceptability of EDAM by end-users will be conducted.

Any study assessing the potential performance of such eCDSAs must necessarily be pragmatic and conducted in environments as similar to real-world conditions as possible. Otherwise, healthcare worker prescribing and other management practices may consciously or unconsciously be influenced if such a study were to be conducted in a research-oriented context. Furthermore, for policy-makers to consider wide-scale eCDSA implementation, what is most needed is a pragmatic implementation study of its impact in routine care. As such, this study will evaluate the introduction of EDAM into routine care aiming to improve the management of patients with AFI, with reduction in empirical antibiotic prescribing as the primary outcome of interest. No research staff will be present, and to minimise disruption and alteration of routine care, a waiver of written patient informed consent will be requested from the relevant ethics committees, in accordance with the 2016 WHO/CIOMS International Guidance for Health-related Research Involving Humans,[11] and as has been practiced in previous large cluster-randomised trials for similar interventions.[2]

The CRP rapid test which will be used is the Actim® CRP test from Medix Biochemica (Finland; ISO certification ISO13485:2016).[12] Much like a malaria rapid test, it is a simple lateral flow device that uses capillary blood, obtained through a finger- or heel-prick, and provides a semi-quantitative indication of whether CRP concentrations are <10mg/L, between 10-40mg/L, between 40-80mg/L, or above 80mg/L, in under 5 minutes with minimal training requirements. It meets European Union standards (CE-marking) as well as the regulatory requirements of 13 other countries, and has been validated for accuracy in previous studies.[13 14] The pulse oximeter which will be used is a Lifebox-Smile Train hand-held device, which is specifically manufactured to be durable for use in resource-limited settings,[15] and which we have successfully used in SEACTN RFI Project Work Package A. Lifebox is a non-governmental organization whose goal is to improving anaesthesia safety through the distribution of pulse oximeters developed for use in low-resource settings. Medix Biochemica and Lifebox played no role in the design of this study, and we declare we have no conflicts of interest with

respect to the choice of these point-of-care aids. We will use the SEACTN network of PHCs to conduct this study, bringing in other PHCs as necessary to achieve the total number of clusters required per site.

1.2 Main research question

Can an eCDSA such as EDAM which integrates clinical features, pulse oximetry, with malaria and CRP rapid tests improve routine clinical management of patients with AFI?

1.3 Brief description of the intervention

The implementation of EDAM and the required necessary training will be conducted at primary health-care centres (PHCs), which are the first facility-based access points for public sector primary health services at the study site. After site level randomisation, we will provide further training for healthcare workers in the intervention PHCs on the use of EDAM to guide clinical management, including referral and antibiotic prescribing decisions. The required training will include measuring and interpreting vital signs, oxygen saturation, and CRP levels, as well as safety-netting i.e., information given to patients and/or their carers about actions to take if their condition fails to improve, changes, or if they have further concerns about their health.

1.4 Description of the population to be studied

This study will be conducted in patients presenting with AFI to study PHCs in Battambang province, Cambodia, all of which are in rural areas.

2. OBJECTIVES

2.1 Primary objective

To assess the impact of EDAM (and related training) on the proportion of patients with acute fever prescribed antibiotics in routine primary health care at initial presentation.

2.2 Secondary objectives

1. To compare the proportion of patients with full recovery at 7 and 14 days in intervention and control PHCs.
2. To compare the proportion of patients referred to hospital at presentation in intervention and control PHCs.
3. To determine the compliance of healthcare workers in intervention PHCs with the management recommended by EDAM.
4. To compare the proportion of patients with unplanned re-presentations to any healthcare facility at 7 and 14 days (if not fully recovered by 7 days) in intervention and control PHCs.
5. The proportion of patients prescribed antibiotics by a healthcare provider, or who independently purchased antibiotics, during the follow-up period, as determined by self-report, in intervention and control PHCs.
6. To compare the proportion of patients with severe clinical outcomes (death or hospitalization) at 7 and 14 days (if not fully recovered by 7 days) in intervention and control PHCs, not including those referred to hospital at presentation.
7. To determine the proportion of patients prescribed an antibiotic in intervention PHCs by CRP level (<10 mg/L, between 10 and 80mg/L, >80 mg/L), and compare these with prescribing rates across the same CRP ranges as documented in SEACTN RFI Project Work Package A.
8. To evaluate the usability and acceptability of EDAM for healthcare workers
9. To assess the cost-effectiveness of EDAM compared to routine care.

3. STUDY DESIGN

3.1 Design

A pragmatic, cluster-randomised controlled trial with two study arms consisting of 15 PHCs in the intervention (EDAM-guided clinical management) arm and 15 PHCs in the control (standard care) arm. A PHC will be considered as a cluster. The pragmatism of the study was confirmed using the PRagmatic Explanatory Continuum Indicator Summary (PRECIS)-2 tool,[16] with the majority of the study design domains rated 'very pragmatic' (Appendix 1).

3.2 Study locations

There will be one study site, comprised of 30 clusters, located in Cambodia. The PHCs will be selected through another longstanding collaboration with the NGO Action for Health Development (AHEAD).

3.3 Primary health centres

At the study site, PHCs deliver most primary care services and national targeted health programs to the population, especially in rural areas. Apart from acute care, services provided by PHCs include hygiene, vaccinations, antenatal care, safe delivery and health education.

PHCs selected to participate in this study must meet all the following conditions:

- Have healthcare workers authorised to prescribe antibiotics
- Stock antibiotics
- Are likely to have at least 150 patients present with AFI within a four- to six-month period, verified by checking patient logbooks and/or numbers recruited into the SEACTN observational study

3.4 Patients and eligibility criteria

Healthcare workers will be advised that use of EDAM should be restricted to patients within a recommended target population. This target population comprises patients meeting all the following inclusion and exclusion criteria.

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. A limited version of the app which does not contain the clinical decision support component and which only allows screening and data collection will be used in control clusters.

4. ENDPOINTS/OUTCOME MEASURES

The primary and secondary endpoints/outcome measures for this study are shown in the table below.

Primary endpoint
Proportion of patients with acute fever aged ≥1 year who are prescribed antibiotics in the two study arms
Secondary endpoints
a) Proportion of patients with full recovery at 7 and 14 days in the two study arms. b) Proportion of patients referred to hospital at presentation in the two study arms. c) Proportion of patients in the intervention arm whose management followed the EDAM recommendations. d) Proportion of patients with unplanned re-presentations at 7 and 14 days (if not fully recovered by 7 days) in the two study arms. e) Proportion of patients prescribed antibiotics by a healthcare provider, or who independently purchased antibiotics, during the follow-up period, as determined by self-report. f) 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. g) Proportion of patients prescribed an antibiotic in the intervention arm with: a. CRP < 10 mg/L b. 10mg/L ≤ CRP ≤ 80mg/L c. CRP > 80mg/L h) Measure of usability and acceptability: Structured interviews will be conducted with the healthcare workers in the intervention arm at the end of the study to determine whether EDAM was usable and useful and whether they support its continued use (a separate ethical approval application will be made for this work). i) Measure of cost-effectiveness: A cost-effectiveness analysis will be carried out to assess the budget implications for introducing EDAM

5. STUDY PROCEDURES

5.1 EDAM app overview, screening, and recruitment

PHCs will be randomly allocated to intervention or control arms using a computer-generated random allocation procedure. All PHCs will be provided with a sufficient number of tablet devices loaded with the EDAM app (full version for intervention arm PHCs and limited version for control arm PHCs). Screening, recruitment, and data collection for the study will be integrated within this app.

Intervention arm PHCs will be provided with the full version of the app capable of executing all three functions in addition to the clinical decision support algorithm, the basic structure of which is shown in Appendix 2. Control arm PHCs will have a simplified version that does not contain the clinical decision support algorithm but is able to perform the other functions, including collecting data on symptoms and antibiotic prescribing.

Only patients presenting acutely to study PHCs i.e., those without scheduled appointments will be screened for eligibility. The app will use skip logic and contain prompts for the healthcare worker to check patient eligibility, allowing recruitment and data collection only when the requisite conditions are met.

Patients can be enrolled multiple times during the study period, as the primary objective is to determine the proportion of presentations which result in antibiotic prescription. However, they cannot be re-enrolled if they are within the follow-up period, as any attendances within this period will be logged as unscheduled re-presentations. This is a secondary outcome measure. If all the following identifiers of a patient are exact matches with those of another patient currently under follow-up, the healthcare worker will confirm that they are not the same person: date of birth (or age if date of birth is not known), gender, and village of residence. Only once this confirmation is provided can the patient be enrolled. **5.2 Clinical assessment**

All patients will have a medical history taken and will be examined as per normal practice. In intervention arm PHCs this process will be more structured as it will be guided by EDAM. Practice will remain unchanged in control arm PHCs.

5.3 Pre-commencement community and health worker engagement and education

Before randomization of participating PHCs, we will present an overview of the study to all PHC healthcare workers and provide education about the role of antibiotics, AMR, and identification of clinical signs of severity, as well as good clinical practice (GCP) for research. Community consultation has already taken place prior to the commencement of SEACTN RFI Project Work Package A, and further community engagement activities using the same proven approaches will be undertaken to explain the study and its potential benefits.

5.4 Intervention and EDAM app training

As stated previously, the intervention is the EDAM app, which is an eCDSA that integrates clinical features, pulse oximetry, with malaria and CRP rapid tests to guide primary healthcare workers in their clinical decision-making when confronted with participants with AFI, and training required for effective use of the app. This training will include familiarisation with the app interface, as well as measurement and interpretation of vital signs, CRP rapid tests, and pulse oximetry. The process by which the app has been developed and the evidence base for its development have been described in section 1.1.

Upon presentation to intervention arm PHCs, participants will have their demographic details logged on the EDAM app. Eligibility for the study will be assessed (see eligibility criteria in section 3.4), following which, if the patient is eligible for enrolment in the study, one or more healthcare workers will record vital signs, including measurement of peripheral oxygen saturation using pulse oximetry, and the presence of any observed danger signs. The selection of relevant observed danger signs (e.g., convulsions) will be based on established national clinical guidelines and ratified by a panel of local expert clinicians.

One of three possibilities may ensue:

- The patient meets eligibility criteria and has no measured danger signs (Table 1) or observed danger signs. In this case, the patient will be enrolled, EDAM will recommend a malaria rapid test and then guide the healthcare worker through the in-built algorithm leading to a suggested initial management plan.
- The patient meets eligibility criteria and has one or more measured or observed danger signs. In this case, EDAM will recommend a malaria rapid test and empirical antibiotic prescription, the choice of which will depend on local guidelines, and immediate referral to hospital. The patient will be enrolled and the algorithm will end here.
- The patient does not meet eligibility criteria. In this case, EDAM will inform the healthcare worker that it is not appropriate to be used for this patient and that they should revert to their

usual practice in dealing with non-acutely febrile patients. The patient will not be enrolled and the algorithm will end here.

Intervention arm PHCs will each be provided with two sphygmomanometers and two pulse oximeters to mitigate the possibility of equipment failure. Nevertheless, where the algorithm requires a measurement by a machine it will include an option not to enter a result.

Age group	Measured danger signs
Children aged ≥1 to <5 years	• Voice/pain/unresponsive on AVPU scale • SpO_2 <90% • Severely abnormal heart rate [pulse of <80 or >160 beats per minute]
Children aged 5 to <15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate [pulse of <70 or >150 beats per minute (5 to <12 years) or <50 or >130 beats per minute (12 to <15 years)] • Fast breathing [respiratory rate of ≥40 breaths per minute (5 to <12 years) or ≥30 breaths per minute (12 to <15 years)] • SpO_2 <90%
Adults aged ≥ 15 years	• Voice/pain/unresponsive on AVPU scale • Severely abnormal heart rate (pulse of <40 or >140 beats per minute) • Fast breathing (respiratory rate of ≥35 breaths per minute) • SpO_2 <90% • Systolic blood pressure <90 mmHg

Table 1. Measured danger signs by age group.

As can be seen from the above, all eligible patients will have a malaria rapid test administered early if they meet eligibility criteria following measurement of vital signs, as is routine for all febrile patients at the study site. If the test is positive, they will be treated with an anti-malarial, the choice of which is dependent on national guidelines. However, it is immediately obvious that the structured approach of EDAM, as well as its capability to formulate diagnoses and recommend management for non-malarial AFI, extends the current paradigm of malaria-focused AFI management.

CRP rapid tests will be recommended to guide antibiotic prescription at appropriate points in the eCDSA in patients with no danger signs. As described previously, these are semi-quantitative tests with threshold values of 10, 40, and 80 mg/l. If a CRP test is recommended and performed, the following guidance will be given to the healthcare worker:

- CRP <10 mg/l: reassure the patient that antibiotic prescription is not indicated.
- CRP >80 mg/l: antibiotic prescription, the choice of which will depend on local contexts.
- CRP 10–80 mg/l: reassure the patient that antibiotic prescription is not indicated, unless there is concern based on the clinical judgement of the healthcare worker that the patient would suffer an adverse outcome if antibiotics were not prescribed.

Safety-netting will be recommended for all patients in the intervention arm not being referred, and healthcare workers in both arms will be provided training on how to do this.

The autonomy of healthcare workers will be maintained, in that they will be allowed to use their discretion and clinical judgement regarding the suggested diagnoses and initial management. EDAM is not intended to be prescriptive, but merely a guide to help healthcare workers in their decision-making. We recognise that there may be healthcare workers who are more experienced or have higher skill levels than others, and that decision-making may be influenced by factors other the objective

ones considered in EDAM. Where a healthcare worker does not agree with the suggested diagnosis and management, the app will collect data on their reasons so that these can be analysed with the goal of improving future versions of EDAM. It will be emphasised to healthcare workers that overriding the EDAM recommendation is entirely acceptable and that collecting information on the reasons for this will provide important input in future improvement of the algorithm.

Healthcare workers in intervention arm PHCs will be provided with face-to-face training on the use of EDAM. They will also be taught how to use pulse oximeters and CRP rapid tests, which are not available in control arm PHCs, as well as trained on measuring blood pressure, respiratory rate, and pulse rate, and assessing level of consciousness. Training will be conducted by the study team in the relevant local language prior to patient recruitment, with refreshers conducted on the advice of site coordinators or study monitors. Contact details of the study coordinator and/or field supervisor will be provided to PHCs; these personnel will be available for advice should any queries regarding the study arise.

5.5 Clinical/laboratory/other procedures

Malaria rapid tests are already available at all PHCs as part of standard care, although brands may vary between countries. In addition, semi-quantitative lateral flow CRP tests will be available for healthcare workers to use in eligible patients at intervention PHCs when prompted by EDAM. If a patient agrees to these tests, a finger prick blood sample will be taken by the healthcare worker and placed onto the test kit in accordance with manufacturer instructions. Refusals will be recorded in the EDAM app. Other than these finger prick samples, no others will be taken. CRP test kits and associated consumables will be re-stocked on a monthly basis and checked to confirm they are properly used for study purposes only. The training for healthcare workers will emphasise respect for patient autonomy and that refusal on their part to be tested should be accepted without reservation. Reasons for patient refusal to be tested will be noted in the app to inform future algorithm development and community engagement activities.

5.6 Follow up

Patients will be followed up by telephone at 7 days post-presentation (allow +2 days); patients who have not recovered by day 7 will be followed up at day 14 (+2 days)**.** The following data will be collected at follow up:

- Survival
- Recovery (self-reported)
- If not recovered, whether symptoms were better, worse, or the same
- Whether they re-presented to another healthcare provider (re-presentations to the same PHC should be captured by the EDAM app)
- If they re-presented, whether they were hospitalized and (if known) whether antibiotics were prescribed

Should a patient be uncontactable by telephone after three attempts, we will utilize SEACTN village health workers to locate the patient and conduct the follow-up interviews at day 7 and day 14, as necessary. If this is unsuccessful, the patient will be deemed lost to follow up.

5.7 Withdrawal/discontinuation criteria

Participants have the right to withdraw consent for follow-up at any time. In addition, investigators may discontinue a participant from the study at any time if the investigator considers it necessary for any reason, including but not limited to:

- Ineligibility (either arising during the study or having been overlooked during screening)

- Significant protocol deviation
- Significant non-compliance with study requirements

The reason for withdrawal will be recorded in the participant's study file. Data from withdrawn participants will be included in the intention-to-treat (primary) analysis but not in any per protocol analyses.

5.8 Minimization of error and bias

To reduce bias within healthcare providers, cluster randomisation will be used. The study will be run until the recruitment target for each cluster is met, which is likely to be approximately six to nine months.

Data collection will be performed electronically using the EDAM app. This will allow inbuilt checks to minimise error, for instance by having pre-specified ranges for vital sign measurements. Additionally, because data will be transmitted in real time or near-real time to the central server, data cleaning will occur prior to the conclusion of the study allowing for earlier detection and correction of errors if necessary.

5.9 Serious adverse events monitoring

While the research is low-risk, a Data and Safety Monitoring Board (DSMB) will, nonetheless, be convened. Further details of the DSMB are provided in section 9.8.

6. STATISTICAL ANALYSIS

6.1 Description of statistical methods

Analysis of the primary endpoint

The primary endpoint of this trial is the proportion of patient consultations for AFI which result in antibiotic prescription. The primary comparison between the treatment arms will be a logistic regression with the treatment assignment as a fixed effect, and the PHC as a random effect. *P*-values (two-sided) below 0.05 are considered significant. A two-sided 95% confidence interval (CI) for the odds ratio of being prescribed antibiotics (the primary endpoint) will be calculated.

The primary endpoint (proportion of patients given an antibiotic prescription) will also be investigated by subgroup to assess whether any change in antibiotic prescribing is homogeneous across subgroups. Specifically, intervention effects and appropriate tests for heterogeneity will be calculated in the following pre-defined subgroups:

- Age (younger children aged ≥1 to <5 years, older children aged 5 to <15 years, and adults aged ≥15 years)
- Sex
- PHC
- Patients with a documented fever or hypothermia at presentation vs. patients without.

Analysis of secondary endpoints

Secondary endpoints (a) to (f) as per Section 4 will be analysed in a similar manner to the primary endpoint.

A detailed Statistical Analysis Plan (SAP) will be developed prior to the completion of recruitment for the study.

6.2 Sample size calculation

There is scant reliable routinely collected data on antibiotic prescription in the study PHCs. We have based the baseline rate of antibiotic prescription on the findings, to date, of the SEACTN RFI Project Work Package A, which includes PHCs where the proposed trial will be run,[7] where data on patients prescribed antibiotics for AFI has been systematically collected since 2021. In the PHCs at the study site which are participating in this planned interventional study, the mean proportion of acutely febrile patients prescribed antibiotics was approximately 25%. Based on the findings of the ICAT cluster-randomized trial, where the use of CRP rapid tests reduced the antibiotic prescription rate by 36%,[2] we estimate that EDAM will result in a reduction of antibiotic prescription from 25% to 17.5%.

All PHCs participating in SEACTN RFI Project Work Package A will also participate in this study. Other PHCs which see a broadly similar number of patients per month as these PHCs will be selected for inclusion in this study, to make up a total of 15 PHCs each in the control and intervention arms and on the assumption that their antibiotic prescription rates are also broadly similar. Each PHC will be treated as a cluster. Given the above, the sample size calculations are based on probabilities of 0.05 and 0.2 for Type I and Type II errors, respectively, and an intra-class correlation coefficient of 0.025 as is common for cluster randomized trials of this nature.[4 17]

Based on the parameters mentioned previously, with 15 clusters per arm the target number of patients to be recruited per cluster is 152 whilst assuming a drop-out rate of 10%. In total, therefore, the target number of patients to be recruited is 4560. Sample size calculations were performed in Stata 18 (College Station, USA).

The study is not powered to detect differences within each age group, but subgroup analyses will be conducted among patients aged ≥1 to <5 years (younger children), 5 to <15 years (older children), and ≥15 years (adults), as mentioned previously. While inclusion of safety endpoints as co-primary objectives was also considered, based on SEACTN RFI Project Work Package A data the absolute risk of a severe outcome, defined as death or hospitalisation for longer than three days or persistent symptoms at 28 days post-presentation, is very minimal (approximately 1.5%).

7. DATA MANAGEMENT

7.1 Data collection

As mentioned previously, healthcare workers will be trained prior to study commencement on collection of data using the version of the EDAM app relevant to their PHC. Training materials will be uploaded to the tablet devices in case they need to refer to these.

Data collection will occur in the EDAM app, as described in section 5.1.

7.2 Data coding

Patients will be assigned a unique composite ID number for the study each time they are enrolled.

Patients will be classified by diagnosis, presence of danger signs, antibiotic prescription at presentation, as well as clinical and other secondary outcomes. Healthcare workers will be asked to specify their working diagnosis and degree of confidence in their diagnosis on an ordinal scale.

One important caveat is that patients who re-present during the follow-up period will be considered as unscheduled attendances secondary to the initial diagnosis, given that we are interested in assessing the frequency of unscheduled attendances and how EDAM impacts this metric. It will also allow us to see whether antibiotics are initially withheld and then given at a subsequent visit. The major limitation of this approach is that some patients may be categorised as unscheduled presentations when their subsequent visit is actually for a new problem or illness.

A data dictionary will be constructed in which all variables are clearly explained.

7.3 Access to data

After entry into the electronic data environment, data will be uploaded to a central database. Access to data will be password protected. Direct access will be granted to authorised representatives from the University of Oxford, the study site partners, and the respective national ethics committees for monitoring and/or audit of the study to ensure compliance with regulations.

7.4 Data handling and record keeping

Data will be captured electronically through the relevant sections of the EDAM app and submitted to the central cloud server. A logbook of patients screened and recruited will also be maintained. The only patient-identifying data entered in the logbooks will be the names of patients, their villages of residence, and their telephone numbers, for the purposes of carrying out follow-up. No other identifiers will be collected.

Electronic data will not be modifiable by the healthcare worker after submission to the server, although authorised users e.g., site research staff will be able to for data cleaning purposes. The database and all electronic data will be backed up daily, with weekly off-site storage. In accordance with MORU Standard Operating Procedures (SOPs), de-identified electronic data will be stored indefinitely on the central server, while paper records will be preserved for five years. Anonymised stored data may be shared with other researchers for future use according to the terms defined in the MORU data sharing policy (MORU Tropical Network Policy on Sharing Data and Other Outputs — MORU Tropical Health Network (tropmedres.ac).

7.5 Dissemination of results

Results will be used to inform the design of implementation strategies as well as policymaking decisions. Results will be written up for publication in peer-reviewed journals and communicated as part of scientific meetings, as appropriate and as agreed by all members of the study team (PI/sponsor). A trial protocol paper for the main intervention study i.e., excluding the stakeholder and economic analyses will also be published.

8. QUALITY ASSURANCE PROCEDURES

Electronic data checks and field restrictions will prevent errors with extreme values being entered. Further internal checks of the entered data will be done to look for outliers and errors.

The study will be conducted in compliance with this protocol, International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) and any applicable regulatory requirement(s). Staff involved in data collection, interviews, transcription and data coding will be appropriately qualified to perform assigned tasks and will be trained on study procedures prior to start of the study. Monitoring will be overseen by the MORU Clinical Trials Support Group (CTSG) to ensure compliance to the study protocol and applicable guidelines and regulations.

Data validation will be performed to identify errors and thus ensure completeness, validity and data accuracy.

9. ETHICAL CONSIDERATIONS

9.1 Ethical review

The trial protocol will be submitted for external peer review by the ethical review body/institutional review board with responsibility for the site, this is being the Battambang Provincial Health

Department Ethics Committee in Cambodia, in addition to review by the Oxford University Tropical Research Ethics Committee (OxTREC). If required, permission to carry out this study also will be obtained from local health authorities.

Amendments

All amendments and modifications will be submitted to the institutional IRBs listed above for review and approval. No changes in protocol conduct will be implemented until approvals by all IRBs are obtained.

Continuing review reports

Where necessary, the Principal Investigator will be responsible for submitting the required continuing review report(s) and associated documents to the relevant IRBs, allowing sufficient time for review and continuation documentation prior to the established continuing review date. A closeout report will be submitted according to ethics guideline.

Managing and reporting protocol deviations

Any deviation from the protocol that may have an impact on the safety or rights of the participant or the integrity of the study will be promptly reported to the appropriate IRBs within the required timeframe from which the deviation is identified. All other deviations will be similarly reported to the appropriate IRBs within the required timeframes.

9.2 Informed consent

A waiver of written individual informed consent from patients (or that of a legally authorized representative) to participate in the study will be requested from the relevant ethical review boards, to ensure as little disruption of routine practice as possible. This is in accordance with the 2016 CIOMS Guideline 10,[11] which states that in the following circumstances a waiver of informed consent could be applied:

- if the research would not be feasible or practicable to carry out without the waiver or modification;
- if the research has important social value; and
- if the research poses no more than minimal risks to participants.

The proposed study and intervention meet all these criteria. The research question relates to the impact of EDAM on clinical management of AFI in a routine care environment, therefore extensive informed consent procedures by research staff or the local healthcare workers on site could alter prescribing behaviour. This would directly affect the primary outcome and make us unable to answer our research question because we would no longer be operating in a routine care environment. Sim and Dawson argue that waiving informed consent is justifiable when the methodological integrity of the study is brought into question.[18] Taking written informed consent would also disrupt patient care. In order for healthcare systems to be responsive and improve patient care implementation, studies are required to generate evidence for policy change and to ensure that the benefits seen in research settings are translated into routine care. There is precedent for this waiver, as illustrated by a similar cluster-randomized trial performed recently in Vietnam.[2]

However, verbal assent will be taken for follow-up. It will also be obtained before collecting finger prick blood to be tested for malaria and CRP when required by the algorithm as part of the management plan, as is usual in clinical practice. This verbal assent will recorded in the EDAM app.

The research question is of high importance and social value, with AFI being a leading cause of often unnecessary antibiotic prescribing in the community, a key driver of AMR. The use of EDAM may also

help to identify those patients who need hospital referral and/or antibiotics but may be missed by routine clinical assessment. Lastly, the components of EDAM, namely pulse oximetry, malaria and CRP rapid tests, and clinical symptom-based guidelines have each individually been determined to be of minimal risk and are already widely used for these purposes in other settings; furthermore, large clinical trials of similar, but not identical, eCDSAs with extensive patient follow-up have previously been conducted in primary care settings elsewhere.[6 10] The drawing of finger prick blood for malaria and CRP rapid tests is also of minimal risk and the blood taken is only being used for direct patient care. Similar to other tests that may be indicated, patients or their legal guardians will be able to refuse these tests, without any other impact on their care.

9.3 Participant confidentiality

As described in the data collection section, each patient will be assigned a unique study number which will be used in data entry and the database in order to protect the patient's identity. Patients will be identified only by their unique identifier on study documents and any electronic databases. However, to enable follow up each PHC will record names, villages of residence, and telephone numbers into a designated logbook for use only at that location; these details will not be entered into any databases held or accessed by the study team. All documents will be stored securely and only accessible by study staff and authorised personnel. Any scientific publications or reports will not identify any individual participant/s by name or initials.

9.4 Potential risks of participation

The risks of participation are low. Firstly, measurement of oxygen saturation using pulse oximetry is now considered the 'fifth vital sign' and is recommended by the WHO when possible in rural LMIC primary care settings,[19-21] therefore its use is not controversial. Secondly, symptom- and vital sign-based diagnostic algorithms, such as the Integrated Management of Childhood Illness guideline, are also widely used in clinical practice. Lastly, MORU has previously conducted a large clinical trial on CRP-guided treatment in patients with AFI with extensive patient follow up, demonstrating that it is effective in reducing antibiotic prescribing and did not adversely affect patient outcomes.[22] A decision support tool integrating all three would, therefore, not be expected to pose a risk to patient safety. Healthcare workers in the intervention arm are also able to use their discretion if they do not agree with the management recommended by EDAM. Additionally, as an extra safeguard, they will be trained to provide safety-netting to all patients they recruit.

To reiterate, we do not foresee major risks of harm from participating in this implementation study, although there may be possible mild discomfort while taking finger prick blood for malaria and CRP rapid tests. The potential risks of using confidential data will be minimised by anonymisation.

9.5 Benefits of study participation and the wider community

Currently, given the low clinical diagnostic and management skill levels of rural primary healthcare workers in the study site, hospital referral and antibiotic prescribing is poorly targeted. This leads to potential inappropriate referral and burdening of secondary care, inappropriate antibiotic prescribing such as to patients in whom antibiotics are not indicated or the prescription of an antibiotic not appropriate to the clinical syndrome, and non-identification of patients whose care should be escalated and/or to whom antibiotics should be prescribed. Furthermore, unnecessary use of antibiotics exposes patients to the risk of adverse effects, and is known to increase the risk of subsequent acquisition of resistant infections, as well as destruction of the microbiome with a host of associated adverse outcomes. EDAM addresses all these issues in an easy-to-use, tablet-based app, and this study will provide information on its effectiveness in streamlining patient management,

including better antibiotic stewardship which will reduce the prevalence of antibiotic resistant bacteria in the population, and preserving antibiotics for treating serious bacterial infections. There will be no other direct benefits to participants for taking part in this study.

9.6 Payments and inducements

No payments or inducements to patients will be made.

9.7 Use of stored human specimens

No specimens will be stored for further use.

9.8 Study oversight

In line with the principles guiding data and safety monitoring in pragmatic clinical trials,[23] an independent DSMB will be assembled prior to the commencement of the trial. The DSMB will review the protocol and review unblinded data at time points at their discretion. The independent and voting members of this committee will be comprised of between three and five members. The chair will be medically qualified (Prof Piero Olliaro, Worldwide Antimalarial Resistance Network) and at least one of the other members of this committee will be a statistician (Dr Ronald Geskus from the Oxford University Clinical Research Unit, Vietnam). Should there be an even number of members then the chair will have the casting vote.

Given the pragmatic nature of this simple intervention, we will undertake remote monitoring in order to confirm the quality of the research performed to assess and ensure the robustness of the trial results. A monitoring plan will be developed prior to study start.

10. FUNDING

The funders of this study are the Wellcome Trust and the Australasian Society for Infectious Diseases. The manufacturers of the rapid tests used in the study and their agents or distributors have no role in study design or funding. The investigators have no financial or other conflicts of interest.

11. INSURANCE

The University of Oxford has a specialist insurance policy in place (through Newline Underwriting Management Ltd, at Lloyd's of London) which would operate in the event of any participant suffering harm as a result of their involvement in the research.

12. SPONSOR

The sponsor for this study is the University of Oxford.

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APPENDICES

Appendix 1: Completed PRECIS-2 Toolkit

PRECIS-2 toolkit

We would be very grateful if users would give us feedback on using PRECIS-2: just click on "Contact us". These PRECIS-2 criteria are constantly being reviewed and we welcome your input.

How to use PRECIS-2 - Designing trials that are fit for purpose

We think there are four steps to using PRECIS-2, which may be iterative depending on what youdiscover after going through the steps.

Step 1: Why are you doing your trial?

Your first step is to be clear about why you are doing your trial. Are you:

1. Aiming to take an explanatory approach to answer the question 'Can this intervention work under ideal conditions?'
2. Aiming to take a pragmatic approach and answer the question 'Does this intervention work under usual conditions?'

Both approaches to trial design have their place but trialists should be clear which path they are on. As Schwartz and Lellouch pointed out, trialists have often taken the first approach by default rather than as a considered judgement.

Step 2: Consider your trial design choices for each of the nine PRECIS-2 domains

This step is explained in more detail for each domain later on.

Step 3: Score 1 to 5 for these choices made in Step 2 and/or mark on the PRECIS-2 wheel

Having considered your design choices in Step 2, the PRECIS-2 wheel is used to record how pragmatic or explanatory these choices are for each domain. Each domain is a 5-point Likert scale:

1. Very explanatory
2. Rather explanatory
3. Equally pragmatic/explanatory
4. Rather pragmatic
5. Very pragmatic

A table can be used in conjunction with the PRECIS "wheel" or instead of the wheel to give rationalefor scores. You can use this to assist discussion with trial collaborators.

Step 4: Review your PRECIS-2 wheel

Review your design choices (Step 2) on the PRECIS-2 wheel to see whether they will produce a trialthat will support the aim identified in Step 1. Go back to Step 2 and modify your design choices if required.

PRECIS-2 wheel

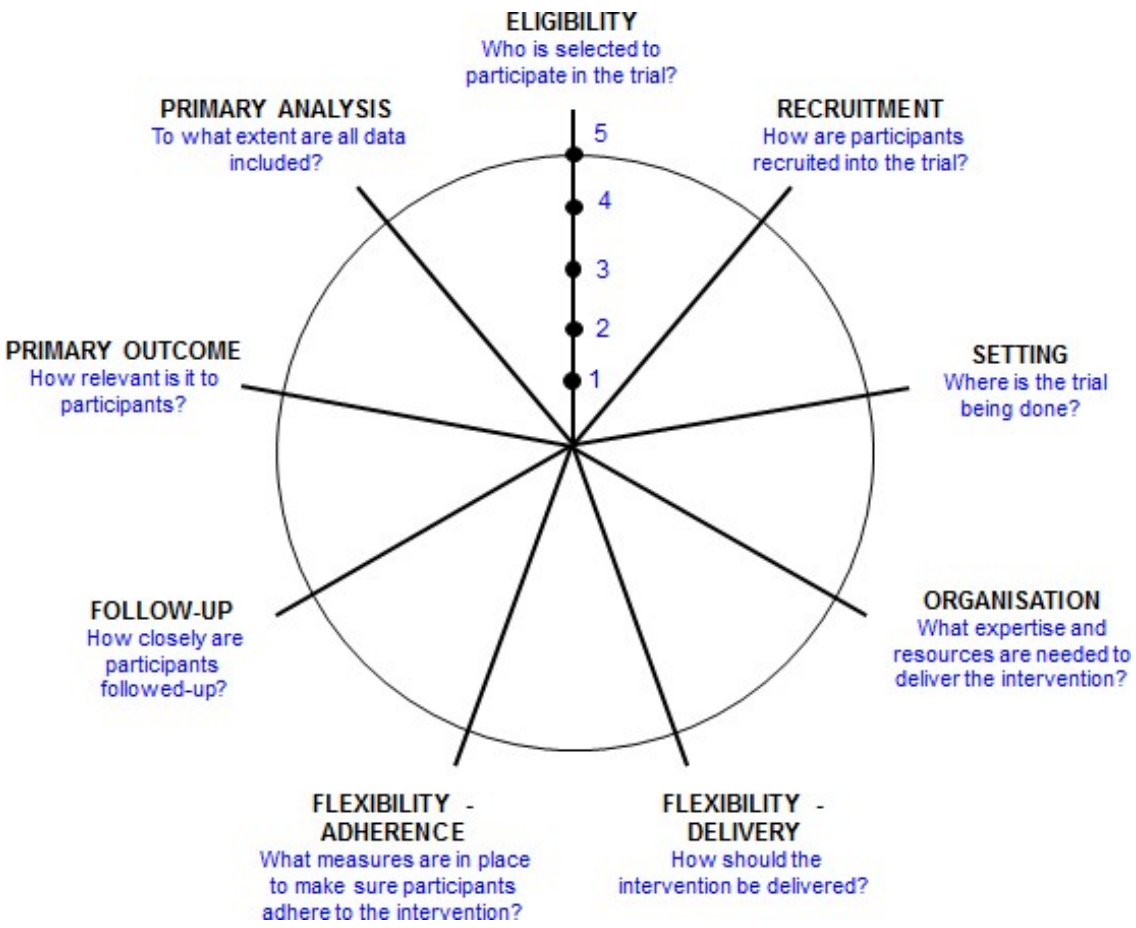

Table 2: PRECIS-2 scores for trial domains

	Domain	Score	Rationale
1	Eligibility Criteria	5	The goal of the intervention is for it to be incorporated as part of routine care for patients with acute febrile illness in rural South and Southeast Asian primary health centres, therefore all patients who present with acute fever will be eligible. The only exception is neonates, for whom fever necessitates referral to secondary care as per well-established guidance.
2	Recruitment Path	4	Patients will be pragmatically recruited as they present to study facilities, with written consent waivers sought from the relevant ethics committees. Healthcare workers will, however, receive compensation for the time taken to enroll and follow up patients, at site where this is necessary to the successful running of the trial. This may involve per capita payment for each recruited patient.
3	Setting	5	The trial and usual care settings are identical i.e., rural Southeast Asian primary health centres.
4	Organisation intervention	5	The trial uses identical organization to usual care, in that the same healthcare workers who normally work at the primary health centres involved in the trial will be those using the intervention (or continuing with the current standard of care if working at a primary health centre in the control arm).
5	Flex of experimental intervention – Delivery	5	While healthcare workers in the intervention arm are recommended to follow the recommendations of the EDAM app, there is no compulsion to do so and their clinical judgement will remain paramount.
6	Flex of experimental intervention – Adherence	5	While healthcare workers in the intervention arm are recommended to follow the recommendations of the EDAM app, there is no compulsion to do so and their clinical judgement will remain paramount.
7	Follow up	3	Not all patients would be routinely followed up, but because some of the secondary outcomes involve events which occur at later time points e.g., recovery at day 7, telephone follow-up is necessary. This follow-up method was chosen to ensure that the nature of follow up is well-balanced between pragmatic and explanatory.
8	Outcome	5	The primary outcome is the proportion of patients prescribed antibiotics. This is of importance to the participants (patients), as well as healthcare workers and the wider health system.
9	Analysis	5	An intention-to-treat approach will be taken for the analysis of the primary outcome, although a per protocol analysis will also be performed in parallel.

The PRECIS-2 Domains

The NINE *PRECIS-2* domains are:

- ***Eligibility*** –to what extent are the participants in the trial similar to those who would receive this intervention if it was part of usual care? For example, score 5 for very pragmatic criteria essentially identical to those in usual care; score 1 for a very explanatory approach with lots of exclusions (e.g. those who don't comply, respond to treatment, or are not at high risk for primary outcome, are children or elderly), or uses many selection tests not used in usual care.
- ***Recruitment*** - how much extra effort is made to recruit participants over and above what thatwould be used in the usual care setting to engage with patients? For example, score 5 for verypragmatic recruitment through usual appointments or clinic; score 1 for a very explanatory approach with targeted invitation letters, advertising in newspapers, radio plus incentives andother routes that would not be used in usual care.
- ***Setting*** – how different is the setting of the trial and the usual care setting? For example, score 5for a very pragmatic choice using identical settings to usual care; score 1, for a very explanatory approach with only a single centre, or only specialised trial or academic centres.
- ***Organisation*** – how different are the resources, provider expertise and the organisation of care delivery in the intervention arm of the trial and those available in usual care? For example, score5 for a very pragmatic choice that uses identical organisation to usual care; score 1 for a very explanatory approach if the trial increases staff levels, gives additional training, require more than usual experience or certification and increase resources.
- ***Flexibility (delivery)*** – how different is the flexibility in how the intervention is delivered and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice with identical flexibility to usual care; score 1 for a very explanatory approach if there is a strict protocol, monitoring and measures to improve compliance, with specific advice on allowed co- interventions and complications.
- ***Flexibility (adherence)*** - how different is the flexibility in how participants must adhere to the intervention and the flexibility likely in usual care? For example, score 5 for a very pragmatic choice involving no more than usual encouragement to adhere to the intervention; score 1 for a very explanatory approach that involves exclusion based on adherence, and measures to improve adherence if found wanting. In some trials eg surgical trials where patients are being operated on or Intensive Care Unit trials where patients are being given IV drug therapy, this domain is not applicable as there is no compliance issue after consent has been given, so this score should be left blank.
- ***Follow-up*** - how different is the intensity of measurement and follow-up of participants in the trial and the likely follow-up in usual care? For example, score 5 for a very pragmatic approach with no more than usual follow up; score 1 for a very explanatory approach with more frequent,longer visits, unscheduled visits triggered by primary outcome event or intervening event, and more extensive data collection.
- ***Primary outcome*** – to what extent is the trial's primary outcome relevant to participants? For example, score 5 for a very pragmatic choice where the outcome is of obvious importance to participants; score 1 for a very explanatory approach using a surrogate, physiological outcome,central adjudication or use assessment expertise that is not available in usual care, or the outcome is measured at an earlier time than in usual care.
- ***Primary analysis*** – to what extent are all data included in the analysis of the primary outcome?For example, score 5 for a very pragmatic approach using intention to treat with all available data; score 1 for a very explanatory analysis that excludes ineligible post-randomisation participants, includes

only completers or those following the treatment protocol.

Notes

“Participants" include patients or other individual recipients of an intervention, and/or providers of the intervention. This may include individual participants and/or one or more levels of clusters. For example, in a trial of a continuing education intervention, participants may be health professionals and trained instructors and the trial may be randomised into clusters at the level of the instructor.

During the design process, if there is uncertainty over how explanatory or pragmatic a domain is, then we suggest the score for this domain should be left blank. This will then highlight uncertaintyand encourage discussion. If PRECIS-2 is used to look at how pragmatic included trials are in systematic reviews then a score of 3 may be chosen if there is inadequate information. This is different to the “3 = equally pragmatic/explanatory”.

Appendix 2: Examples of clinical decision-making algorithms*, by age group

*Local clinicians will review the algorithm and provide input on selection of observed danger signs and local antibiotic prescribing guidelines.

Figure a. Clinical decision-making and management algorithm, children aged 1 to <5

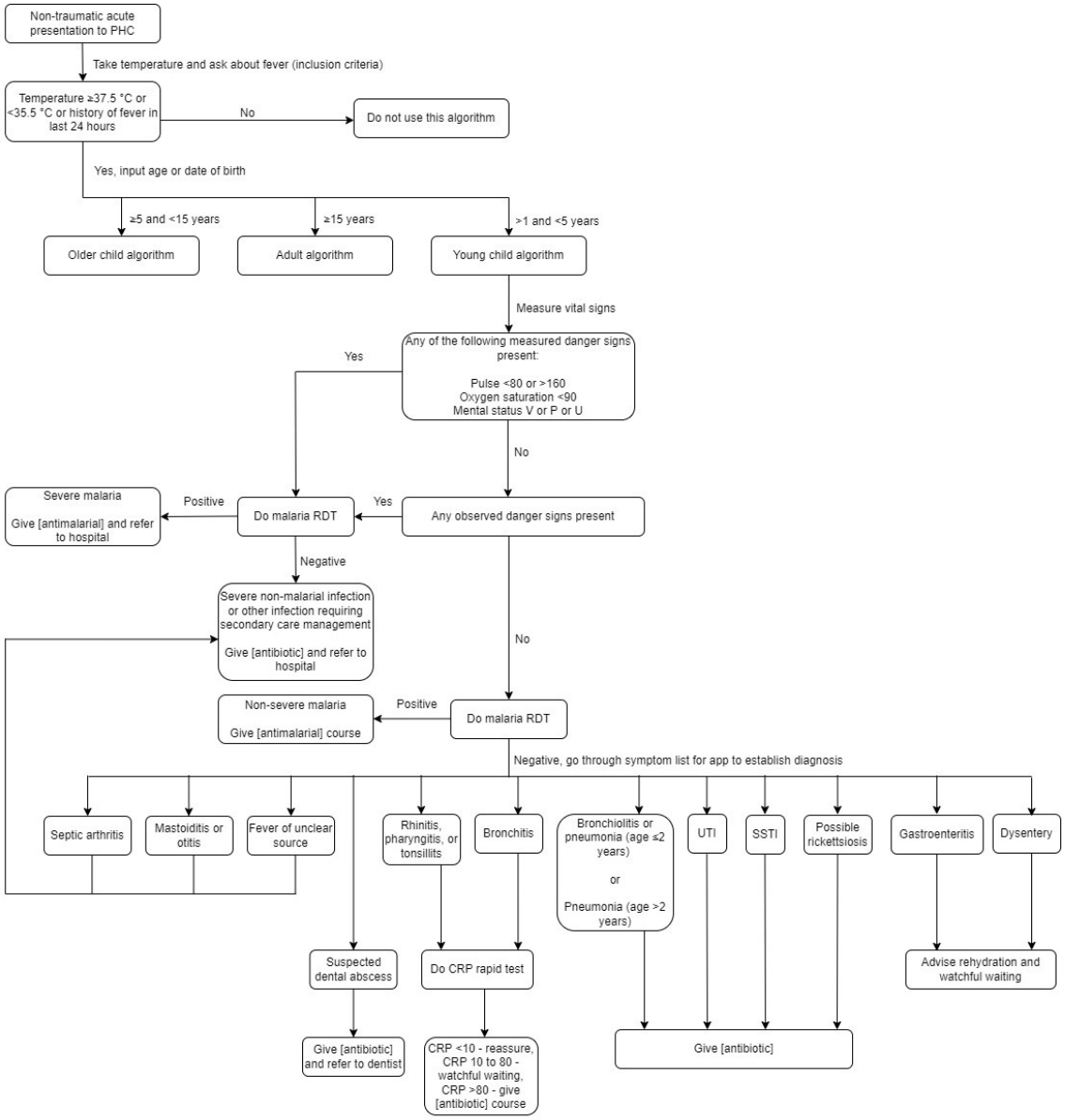

Figure b. Clinical decision-making and management algorithm, children aged 5 to <15

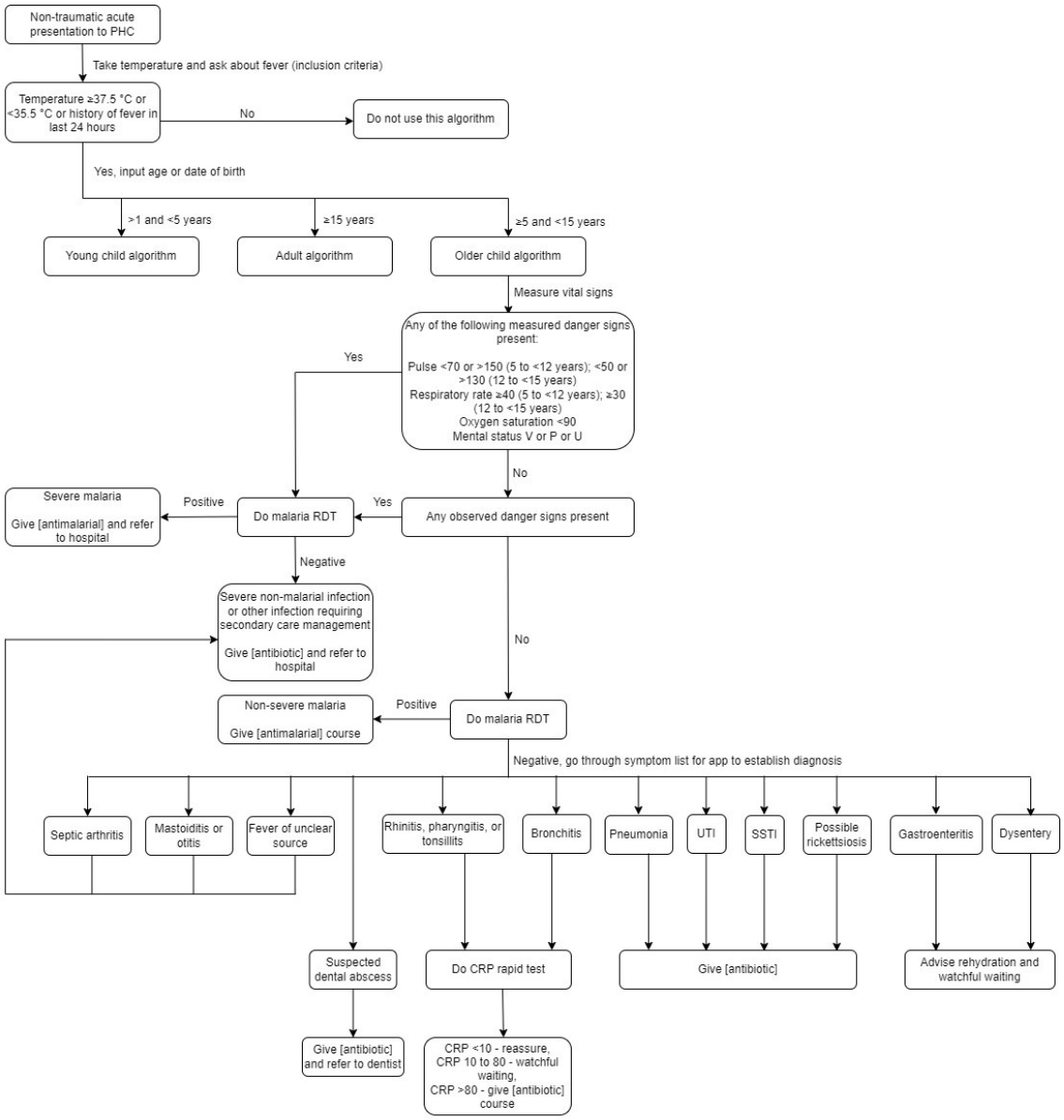

Figure c. Clinical decision-making and management algorithm, adults aged 15 years and older