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DAWA MASTER PROTOCOL

A cluster-randomized trial to assess the effectiveness of a digital clinical decision support system, training and mentorship to reduce inappropriate antibiotic prescribing at primary healthcare facilities in Tanzania

Short title: Digital Antibiotic stewardship and training for Wahudumu wa Afya (DAWA) Project

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Study implementation	- Centre for Primary Care and Public Health (Unisanté), University of Lausanne, Route de la Corniche 21, 1010 Lausanne, Switzerland - Ifakara Health Institute (IHI) – PO Box 78373, Dar es Salaam, Tanzania - Zanzibar Ministry of Health - Zanzibar Health Research Institute		
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VERSION HISTORY

Version Number	Date	Description of Changes	Author(s)
1.0	18.12.2025	**Initial protocol development**	RT, NE, AK, AA, GM
1.1	23.03.2026	**Corrections following IHI IRB review** Section 1: further description of usual care Section 4: Limitations of current CDSAs and the opportunity for integration: mention of ZanEMR Section 7.1: DAWA I cluster Randomized Controlled Trial: further description of usual care P.17, Study setting: description of ZanEMR deployment setting P. 19, Intervention, DAWA I: further description of usual care	AK, NE
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		at day 7. Sections 18.6: adverse events Sections 1, 7.1, 10.1, 11.1, 12.1, 14.1.2, 16.1.1, 16.2.1, 17.2, 18.5.1: revision of DAWA-II related sections Section 12.1: criteria for study site discontinuation	

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Protocol Approval Page

Study Title: A cluster-randomized trial to assess the effectiveness of a digital clinical decision support system, training and mentorship to reduce inappropriate antibiotic prescribing at primary healthcare facilities in Tanzania

Protocol Version: v1.2

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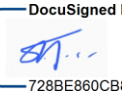
This Master Protocol has been reviewed and approved by the undersigned. By signing below, each signatory confirms that:

- The protocol accurately describes the planned study procedures
- The study will be conducted in compliance with the approved protocol, the principles of Good Clinical Practice (GCP), and all applicable regulatory and ethical requirements.
- Any protocol amendments will be submitted for approval prior to implementation.

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1 PROTOCOL SUMMARY

Scientific Title	A cluster-randomized trial to assess the effectiveness of a digital clinical decision support system, training and mentorship to reduce inappropriate antibiotic prescribing at primary healthcare facilities in Tanzania
Public Title	Digital Antibiotic stewardship and Training for Wahudumu wa Afya (DAWA) Project
Primary registry	To be registered within Clinicaltrials.gov
Countries of Recruitment	Tanzania
Study Setting	Primary healthcare facilities in Zanzibar, Tanzania
Study duration	12months
Health condition	Acute infectious illnesses
Rationale	Inappropriate antibiotic prescribing is widespread in primary care settings and contributes to bacterial antimicrobial resistance (AMR), high morbidity and mortality. Sustainable antibiotic stewardship must address the clinical uncertainty experienced by clinicians, tackle entrenched prescribing habits, and address patient expectations. Building on prior studies and feedback from healthcare providers, this study aims to develop and evaluate a digital clinical support tool integrated within an electronic medical record system, and strengthened mentorship approaches to promote rational antibiotic use in routine primary care settings.
Primary objective	To evaluate the effectiveness of two antibiotic stewardship interventions – both incorporating clinical decision support integrated into an electronic medical record system and one with an additional mentorship/training intervention - to reduce antibiotic prescribing for acute infectious illness in patients of all ages, compared to usual care at primary care health facilities
Study Design	A three-arm, parallel-group, cluster randomized controlled trial (RCT) will evaluate the effectiveness of two intervention packages to reduce antibiotic prescribing compared to usual care. The first intervention integrates digital clinical decision support within the routine electronic medical record system to guide clinicians' decision -making during patient encounters. The second combines this digital support with Antibiotic Stewardship Club Meetings aimed at strengthening provider's knowledge, attitudes, and peer learning around appropriate antibiotic use. Primary healthcare facilities will serve as the unit of randomization, with all patients with an acute infectious illness attending participating facilities during the study period eligible for inclusion. Patient enrollment will occur between months 3-5 after intervention initiation (month 0), once the interventions have been fully implemented and providers are familiar with their use.
Study Population – Key Cluster/Health facility inclusion and exclusion criteria	Inclusion criteria: 1. Government or government designated primary healthcare facilities (dispensaries) open to the general public, providing care to acutely ill children and adults. 2. Health facilities with the Zanzibar Electronic Medical Record system (ZanEMR) available in consultation rooms. Exclusion criteria 1. Health facilities that are planning to be closed for more than 2 weeks during the conduct of the study

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Study Population – Key patient inclusion and exclusion criteria	Inclusion criteria (primary analysis population): 1. Patients of all ages presenting to a participating health facility for their initial consultation related to an acute infectious illness. 2. Patient referred from another health facility Exclusion criteria (primary analysis population): 1. Patients presenting for any other acute non-infectious illness-related consultation, including follow-up consultation (planned or unplanned), chronic care consultation, vaccination consultation, or well-child visit consultation 2. Patient already enrolled in study for a previous consultation
Interventions	**Arm 1: Multifaceted Antibiotic Stewardship Intervention** - Digital Clinical Decision Support integrated within the Zanzibar Electronic Medical Record system (ZanEMR) called ZanEMR-AS (ZanEMR-Antibiotic Stewardship) with initial group training and supported mentorship visits - Audit and Feedback Benchmarking Dashboards - Monthly Antibiotic Stewardship Club Meetings (Months 0-5) **Arm 2: Digital Clinical Decision Support Alone:** - Digital Clinical Decision Support integrated within ZanEMR (ZanEMR-AS) with initial group training and supported mentorship visits - Audit and Feedback Benchmarking Dashboards **Arm 3: Usual Care** - ZanEMR: Routinely used electronic medical record, as implemented by the MOHZ, without clinical decision support features for antibiotic stewardship - Paper and pdf national guidelines including the Zanzibar Standard Treatment Guidelines, international guidelines including IMCI. - Routine supervision by district health management teams
Primary Outcome	Proportion of encounters with an antibiotic prescribed at the day of presentation (day 0)
Secondary Outcomes	**Harm outcomes:** - Proportion of patient encounters for which patient is worse at day 7 - Proportion of patient encounters for which the patient has a severe adverse outcome (composite outcome combining 1) hospitalization without referral, and 2) dead) by day 7 **Secondary antibiotic stewardship outcomes:** - Proportion of patient encounters for which patients use additional medications not prescribed by healthcare provider at the initial encounter by day 7 - Proportion of diagnostic-concordant antibiotic prescribing at day 0 encounters (defined as antibiotic prescribed for a diagnosis requiring an antibiotic, and no antibiotic prescribed for a diagnosis not requiring an antibiotic) - Proportion of patient encounters prescribed an “Access” antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended) among all encounters prescribed an antibiotic - Proportion of encounters with an antibiotic prescribed at the day of presentation (day 0), during month 6 to 11, after the end of antibiotic stewardship clubs and supported mentorship (DAWA-II)

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Subgroup analysis	**Statistically powered key subgroup analysis:** - Patients aged less than five years old **Exploratory hypothesis generating subgroup analyses:** - Patients aged 5 to <15 years old vs patients aged >=15 years old - Self-reported sex (male vs female) - Patients with respiratory infectious illness (vs other infectious illness)

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	- Health facility attendance rate (average number of patients seen per week) - Prescriber cadre (MD, Clinical officer, Nurse)
Main Exploratory outcomes and analyses	- Proportion of patient-encounters prescribed an antibiotic at day 0 in all patients presenting for an acute illness (not limited to those with a presumed infectious illness) - Antibiotic prescription trend over the entire intervention implementation period (Month 0-5)
Sample size	13 clusters and 1,950 patients per arm, for a total of 5,850 patients (including 1,560 patients aged less than 5 years old) within 39 clusters.
Randomization	Randomization will be performed by an independent statistician at the health facility level (cluster level) with a 1:1:1 ratio, stratified by overall baseline antibiotic prescription proportion and attendance rate.
Blinding	Researchers enrolling patients and assessing day 7 outcomes will be blinded. Patients will not be explicitly made aware whether they are attending an intervention health facility but may see antibiotic stewardship commitment posters in health facilities randomized to receiving the antibiotic stewardship club meetings.
Estimated date of first enrollment	1 November 2026
Ancillary / nested studies	Qualitative study: Qualitative methods including in-depth interviews and non-participant observations will be used to determine the feasibility and acceptability of the DAWA interventions by healthcare providers receiving the intervention and stakeholders involved in delivering it. Cost and cost-effectiveness analyses of the interventions will be performed. DAWA III - Before-After analysis: to compare antibiotic prescribing in available health facilities using ZanEMR, not already receiving the ZanEMR-AS intervention within the DAWA I study, at least 4 months before and at least 4 months after the introduction of the antibiotic stewardship features.
Ethics review	To be submitted to: - Ifakara Health Institute IRB, Tanzania - The office of the second vice president of Zanzibar - Zanzibar Health Research Institute (ZAHRI), Tanzania - Cantonal Ethics Review Board of Vaud, Switzerland
Data sharing statement	A de-identified version of the data will be made available upon request through a secure data repository after the publication of the main findings.

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2 STUDY INVESTIGATORS AND COLLABORATORS

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3 ABBREVIATIONS

AMR	Antimicrobial Resistance
AWaRe	Access, Watch, Reserve
CDSA	Clinical Decision Support Algorithm
CDSS	Clinical decision support system
CIOMS	Council for International Organization of Medical Sciences
cRCT	Cluster Randomized Controlled trial
CV	Coefficient of Variation
DHMT	District Health Management Team
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EMR	electronic medical record
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Model
ICC	Intraclass Correlation Coefficient
ICD-10	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
ICEMAN	Instrument for assessing the Credibility of Effect Modification Analyses
ICH	International Council for Harmonisation
ICMJE	the International Committee of Medical Journal Editors
IMAI	Integrated Management of Adults and Adolescent Illnesses
IMCI	Integrated Management of Childhood Illness
INRUD	International Network of Rational Use of Drugs
ITT	Intention-To-Treat
LMIC	Low- and middle- income country
MAR	Missing At Random
MCAR	Missing Completely At Random
NGO	Non-Governmental Organization
PACK	Practical Approach to Care Kit
PRECIS	Pragmatic Explanatory Continuum Indicator Summary
RCT	Randomized Controlled Trial
SAP	Statistical Analysis Plan
SWOT	Strengths, Weaknesses, Opportunities, and Threats
USA	United States of America
WHO	World Health Organization
ZAHRI	Zanzibar Health Research Institute
ZanEMR	Zanzibar Electronic Medical Record System
ZanEMR-AS	Zanzibar Electronic Medical Record System – Antibiotic Stewardship

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4 BACKGROUND AND RATIONALE

Bacterial antimicrobial resistance and inappropriate antibiotic use

Antibiotic prescription is inappropriately high in outpatient primary care settings in low- and middle-income countries (LMICs),[1-6] as well as high-income countries.[7-9] A recent systematic review found that antibiotic prescription in LMICs occurs in 52% of consultations at primary care.[5] Antibiotic prescription rates have progressively increased over the last decade, and is projected to continue to increase over the next years.[10-12] Inappropriate antibiotic prescription is one of the biggest contributors to the development of antibiotic resistance at the individual and population level.[13-15] Consequently, bacterial antimicrobial resistance is directly responsible for 1.3 million deaths a year and rising, as much as malaria and HIV combined.[16,17] The World Health Organization (WHO) has declared it as 'one of the biggest threats to global health, food security and development today'.[18] In addition high antibiotic prescribing is associated with adverse drug reactions, increased healthcare costs and microbiome disruption.[19,20]

With over 80% of antibiotic prescription occurring at primary care,[21,22] the need for antibiotic stewardship programs at the community level is especially important.[23] Indeed one study found that reducing antibiotic prescription at the primary care level had a greater impact on decreasing bacterial antimicrobial resistance than reductions at the hospital level.[24]

Digital health interventions to improve quality of care and antibiotic prescribing

Clinical decision support systems (CDSS) provide clinical guidance at the point of care, ranging from alerts within an electronic medical record (EMR) system, to comprehensive support throughout every step of the consultation process.[25] The later form, often described as clinical decision support algorithms (CDSAs), were developed to help health providers adhere to clinical guidelines.[26] Such tools prompt health providers to collect the necessary clinical information in order for the tool to propose the appropriate diagnoses and treatments based on guideline-derived algorithms. Implemented at primary healthcare facilities in children, CDSAs have shown to improve quality of care,[27-33] and improve clinical outcomes.[32,34,35] In some studies, two to four-fold reduction in antibiotic prescription have been shown without increase in morbidity/mortality,[34-36] while others have shown little to no reduction in antibiotic prescription.[27,37] The drastic difference on the impact of antibiotic stewardship may be due to differences in study design (efficacy versus pragmatic effectiveness studies), epidemiology of study settings, clinical algorithms used, healthcare providers using the tools and supportive training and mentorship associated with the CDSA. The impact of supportive mentorship in part explains the major differences in results between two cluster RCTs evaluating the CDSA ePOCT+ in Tanzania. The study that included frequent targeted mentorship visits using audit and feedback dashboards found a two-fold reduction in antibiotic prescribing.[36] In contrast, the study that had limited mentorship found no reduction in antibiotic prescribing.[38] These findings highlight the potential role of supportive mentorship in enhancing the effectiveness of CDSAs and underscore the need to better understand how such mentorship interventions can be feasibily and effectively implemented in routine care settings.

Limitations of current CDSAs and the opportunity for integration

Despite their potential, many CDSAs have important limitations. Few tools were developed to manage sick outpatients above 5 years old, in fact only one such study was identified by two recent structured and systematic reviews.[26,39] This can frustrate users who are expected to use one digital tool for one age group but not another. Additionally, many CDSAs at primary care operate as standalone tools not

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integrated within existing digital health ecosystems or electronic medical record (EMR) systems. This lack of integration often leads to duplicative data entry and inefficient clinical workflows.[40,41]

Integrating antibiotic stewardship within EMRs in primary care helps address these challenges if done appropriately.[41,42] Such systems can take different forms. Prescription alerts are a well-known example, and while they have their drawbacks (e.g. interruption of clinicians' workflow, alert fatigue), some have been shown to effectively reduce inappropriate antibiotic prescriptions.[43,44] Treatment proposals, are another approach. For example, an electronic order set suggesting conservative (non-antibiotic) treatment is triggered when a certain diagnosis is selected. This strategy has shown promising results, for antibiotic stewardship as well as other domains like safer opioid prescribing.[45,46]

Even more subtle design configurations can influence prescribing behaviors. For example, grouping broad-spectrum antibiotics within the treatment menu options led to fewer such prescriptions, in a Vignette-Based study conducted in the USA.[47] These types of subtle incentives - or nudges - do not restrict or interrupt clinicians, and are appreciated by users for this reason.

In Zanzibar, the deployment of the national EMR system for primary healthcare facilities, called ZanEMR (Zanzibar Electronic Medical Record System), started in 2025, offers a unique opportunity to provide decision support to primary care clinicians.

Mentorship, training, and audit-and feedback interventions to improve antibiotic prescribing

While digital tools can support decision-making, sustained behavior change often requires complementary interventions. Training and education can be an effective way at inducing longstanding clinical behavior change,[48-51] however their effectiveness depends on addressing specific barriers to change.[51,52] Various studies found that single trainings are often insufficient, not allowing enough support or time to process the different stages of behavior change. Multiple trainings sessions and multifaceted interventions – those combining education, mentorship, and feedback are generally more effective than single interventions. [48,49,51,52]

To the best of our knowledge, no study has evaluated the impact of monthly peer-based education meetings among primary healthcare facilities in sub-Saharan Africa. However, a study in China is underway, evaluating monthly peer-based education meetings associated with CDSS.[53] Nonetheless similar approaches, or elements of them, have shown promise in other contexts, including single education peer meetings (Quality circles),[54,55] hospital-based antibiotic stewardship meetings,[56] and audit and feedback interventions.[57,58]

Study rationale summary

Bacterial antimicrobial resistance in part driven by inappropriate antibiotic prescribing is a major public health threat globally and in Tanzania. While digital health interventions such as clinical decision support systems (CDSS) have shown potential to reduce antibiotic prescribing, their impact varies widely across settings. Previous experiences suggest they are most effective if integrated within the national digital health landscape, limits redundant data entry, supports consultations for all patient age groups, and supported by strategies that reinforce clinical behavior change—such as mentorship, training, and audit-and-feedback. However, there is limited evidence from low- and middle-income countries (LMICs), particularly in sub-Saharan Africa, on how to optimally implement and support digital antibiotic stewardship tools at the primary care level. Specifically, it remains unclear whether peer education meetings or routine mentorship visits are more effective in supporting CDSS-driven improvements in prescribing behavior. Building on prior studies and feedback from healthcare providers, in line with the Zanzibar Action Plan on Antimicrobial Resistance,[59] and the Zanzibar Digital Health Strategy,[60] this study aims to develop and evaluate a digital clinical support tool integrated within an electronic medical record system, and strengthened mentorship approaches to promote rational antibiotic use in routine primary care settings.

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5 OBJECTIVES

Primary objective: To evaluate the effectiveness of two antibiotic stewardship interventions – both incorporating clinical decision support integrated into an electronic medical record system and one with an additional mentorship/training intervention - to reduce antibiotic prescribing for acute infectious illness in patients of all ages, compared to usual care at primary healthcare facilities (table 1)

Table 1: Primary objective outline

Population	Patients of all ages attending a primary healthcare facility for their initial consultation related to an acute infectious illness episode (not a re-attendance consultation)
Intervention	1) Antibiotic stewardship clinical decision support integrated in an electronic medical record system with routine mentorship support, feedback & audit benchmarking dashboards, and monthly peer education training on antibiotic stewardship for healthcare providers (6 sessions, taking place from M0 to M5) 2) Antibiotic stewardship clinical decision support integrated in an electronic medical record system with routine mentorship support and feedback & audit benchmarking dashboards
Comparator	Usual care (electronic medical record system without antibiotic stewardship decision support)
Primary outcome	Prescription of an antibiotic
Time point of main interest	Initial consultation (Day 0)
Summary measure	Absolute difference and risk ratio

Secondary objectives:

Harm: To evaluate that there is no more harm to patients managed in intervention health facilities compared to patients in the control health facilities in terms of worse self-reported clinical status, and severe adverse outcome (hospitalization without referral or dead by day 7)

Feasibility and acceptability: The objective is to determine the feasibility and acceptability of the DAWA interventions by primary healthcare workers receiving the intervention and stakeholders involved in delivering the intervention, as well as determinants of rational antibiotic prescribing by primary healthcare workers exposed to the intervention.

Health Economics: The objective is to perform a cost and cost-effectiveness analysis on the impact of the interventions.

Comparative Effectiveness: The objective is to compare the two different interventions (Clinical decision support, 6 mentorship/training sessions with routine mentorship support vs clinical decision support and routine mentorship support) in terms of their impact on antibiotic prescribing and costs.

Other secondary objectives are to compare the intervention arms with control for the secondary outcomes stated in section 11.

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6 PATIENT & PUBLIC INVOLVEMENT IN STUDY DESIGN

The initial study design and intervention design was based on feedback from healthcare providers, patients, and government stakeholders during the conduct and stakeholder engagement of two previous digital health studies in Tanzania.[36,38] Specifically, within the DYNAMIC Tanzania study, over 100 community engagement meetings with over 7,000 participants were conducted, that notably influenced the decision to include adult patients as well as children. Informal and formal feedback from healthcare providers during the conduct of both studies, emphasized the need for the digital health intervention to be integrated with the electronic medical record system, to limit the time required to use the tool, to be aligned with local guidelines, and to integrate clinical benchmarking dashboards to compare their performance with other healthcare providers.

A formal inception meeting as well as individual targeted meetings were held with various stakeholders in 2025, including representatives from the Ministry of Health of Zanzibar, the Zanzibar Health Research Institute, Zanzibar's chief pharmacist, district medical officers and healthcare providers from dispensaries and health centres, as well as NGOs active in digital health and antibiotic stewardship. Feedback from these meetings confirmed that the fight against antibiotic resistance, and therefore against excessive prescription, is a priority for the Ministry of Health as well as for the various stakeholders in the sector. This also confirms the relevance of using antibiotic prescription as our primary outcome. These meetings also highlighted the value of digital health clinical decision support while emphasizing the importance of integrating it within ZanEMR. Finally, they emphasized the importance of collaboration among stakeholders at all levels, leading to the integration of Yahya Mbwana, Ministry of Health Department of Preventive Services Zanzibar, and Muhiddin Omar, Zanzibar AMR focal person, as core members of the DAWA study.

A National health research advisory committee meeting is being put together to be held on a yearly basis including Ministry of Health representatives, members of the National Multisectoral coordinating committee for AMR, members of the technical working group for Antimicrobial stewardship and members of NGOs active in antimicrobial stewardship.

Over 15 primary healthcare providers have already been consulted, informing us on their technical and clinical needs regarding antibiotic stewardship, their priorities during consultations, and their perception of the utility of a digital intervention and antibiotic stewardship club activities. Their input directly guided the design of the interventions and they will continue to be consulted throughout the project to guide future development steps.

Patient representatives will be consulted to provide specific input on:

- Information sheets on study
- Patient screening process
- Outcome selection and definitions, notably harm outcomes and outcome on additional medications taken after the initial consultation
- Dissemination plan

7 STUDY DESIGN

7.1 DAWA I and II - Cluster Randomized Controlled Trial:

The DAWA I study is a pragmatic, three-arm, parallel-group, cluster randomized controlled trial (RCT) designed to evaluate the effectiveness of two intervention packages aimed at reducing antibiotic prescribing in primary care settings (superiority design). A cluster-randomized study design was chosen

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since the intervention is targeted at healthcare providers within specific health facilities, for which randomizing entire clusters (facilities) ensures that the intervention is implemented consistently at the facility level and minimizes the risk of contamination between individuals within the same healthcare setting. The pragmatism of the study was evaluated using the Pragmatic Explanatory Continuum Indicator Summary (PRECIS)-2 tool, that found the majority of the domains rated as "very pragmatic" (see table 2).[61] A random sample of health facilities will be randomly allocated (1:1:1) to the three study arms:

- Intervention 1
  - ZanEMR-AS, digital clinical decision support features integrated within an electronic medical record system, with initial group training and supported mentorship visits
  - Audit & Feedback Benchmarking Dashboards
  - Antibiotic Stewardship Club monthly meetings
- Intervention 2
  - ZanEMR-AS, digital clinical decision support features integrated within an electronic medical record system, with initial group training and supported mentorship visits
  - Audit & Feedback Benchmarking Dashboards
- Usual care (control)
  - ZanEMR: Routinely used electronic medical record, as implemented by the MOHZ, without clinical decision support features for antibiotic stewardship
  - Paper and pdf national guidelines including the Zanzibar Standard Treatment Guidelines, international guidelines including IMCI.
  - Routine supervision by district health management teams

A three-arm study design was chosen to enable the comparison of two intervention approaches with different financial/resource implications, notably the addition or not of the monthly peer education sessions. Patient enrollment for the primary population will occur between months 3-5 after intervention initiation (month 0), once the interventions have been fully implemented and providers are familiar with their use.

Following completion of the primary phase DAWA I, we will continue to collect data over the subsequent 6-month period (months 6-11, DAWA II) to assess the sustainability of antibiotic stewardship practices. During this phase, the following intervention activities will cease: antibiotic stewardship club meetings in arm 1, and support for mentorship visits in arms 1 and 2. Routine mentorship by the District Health Management Team (DHMT) will continue as per usual in all health facilities, including access to antibiotic stewardship audit and feedback dashboards in study arm 1 and 2. The rationale for discontinuing the antibiotic stewardship club meetings, is that by design it is intended to be a 6 month intervention which we hypothesized to be enough to induce long-term change in antibiotic prescribing behavior, while considering resource constraints for generalized implementation.

This will allow to compare antibiotic prescribing rates between each intervention arm and the control arm during the post-intervention period (month 6-12 after start of implementation). The objective is to evaluate whether exposure to ZanAMR-AS, combined with prior supportive mentorship or club engagement, leads to sustained improvements in antibiotic stewardship after the active support phase ends. While the expected effect size is anticipated to be smaller than that observed during the first DAWA I phase, the findings will provide valuable insights into the persistence of behaviour change and the potential from longer-term impact of digital stewardship tools in routine care settings. In addition, the analysis will allow assessment of potential seasonal variations in antibiotic prescribing and illness patterns over the extended follow-up period.

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Table 2: PRECIS-2 scores for trial domains of the DAWA I study[61]

PRECIS-2 Domain	Score (on a 5-point Likert scale)
Eligibility	5 - Very pragmatic
Recruitment	4 - Rather pragmatic
Setting	5 - Very pragmatic
Organisation	4 - Rather pragmatic
Flexibility (delivery)	5 - Very pragmatic
Flexibility (adherence)	5 - Very pragmatic
Follow-up	4 - Rather pragmatic
Primary outcome	5 - Very pragmatic
Primary analysis	4 - Rather pragmatic

7.2 Qualitative studies:

7.2.1 Development of ZanEMR-AS and Antibiotic Stewardship Club

Informal discussions will be held with stakeholders from the Ministry of Health, national advisory committee, clinical experts and primary healthcare workers to guide the development of the different intervention components, especially ZanEMR-AS and antibiotic stewardship clubs. These discussions will not be audio recorded. Verbal consent will be asked to report the inputs provided by stakeholders in scientific publications.

7.2.2 Feasibility and acceptability of the interventions by healthcare providers and stakeholders from the Ministry of Health

To assess the feasibility and acceptability of the interventions, semi-structured In-depth Interviews (IDIs) will be conducted with stakeholders from the Ministry of Health, and healthcare providers from facilities randomized to the intervention arms. Participants will be asked about their perception of the different intervention components, especially ZanEMR-AS and the antibiotic stewardship clubs. For the ZanEMR-AS system, specific attention will be given to its impact on consultation processes, as well as user perspectives on usability, design, and practicality. For the Antibiotic Stewardship Clubs, participants will be asked about the perceived utility of these meetings, potential challenges to participation and the nature of interactions among participants.

In addition, we will conduct non-participant observations of antibiotic stewardship clubs, by systematically observing and documenting the discussions between healthcare providers during the monthly Antibiotic Stewardship Club meetings without directly engaging with or influencing the participants. By maintaining a non-participant role, we aim to minimize observer bias and capture the natural flow of discussions, ensuring that findings reflect authentic experiences. Nonetheless, if statements or behavior of participants at the meetings were not clear, research assistants may ask clarification questions at the end of the meeting to better understand what was meant.

7.3 DAWA III - Before-After Analysis

If the DAWA I cluster RCT demonstrates that the antibiotic stewardship features embedded in ZanEMR (ZanEMR-AS) with or without Antibiotic Stewardship Club meetings shows promise in reducing antibiotic prescribing regardless of statistical significance, then ZanEMR-AS will be scaled across all health facilities using ZanEMR that were not already using ZanEMR-AS during the initial trial.

As part of this broader rollout, refinements to the ZanEMR-AS features will be incorporated based on user feedback gathered during DAWA I and qualitative studies. Following implementation, a Before-

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After analysis will be conducted to assess changes in antibiotic prescribing behavior across the newly exposed facilities. A staggered design will be employed given that the implementation will vary across facilities based on health authorities' decisions and logistical considerations.

The before-after analysis will use routinely collected EMR data to compare antibiotic prescribing rates before and after the introduction of ZanEMR-AS. Facilities with at least 4 months of pre-implementation data and a minimum of 4 months of post-implementation data will be included. This analysis will help evaluate the real-world effectiveness of ZanEMR-AS, under conditions of routine clinical practice, without the potential influence of study-related observation by research assistants present at health facilities in DAWA I (i.e., reduced Hawthorne effect). This substudy will also expand the evaluation to a more diverse set of health facilities, including both health centers and dispensaries, located both in Unguja and Pemba islands, and is powered to detect smaller effect sizes than the DAWA I cluster RCT. It will provide insight into the scalability, durability, and generalizability of digital stewardship tools across varied healthcare settings.

7.4 Cost and cost-effectiveness study

The costs and cost-effectiveness of the two interventions strategies will be compared to usual care. This component of the study will help inform policy decisions on the scalability and value-for-money of the interventions.

7.5 Pre-trial descriptive analyses of routine ZanEMR data

Prior to the start of trial activities, the study team will conduct descriptive analyses of routinely collected clinical data from the ZanEMR to characterize baseline care patterns. These analyses will summarize common diagnoses, antibiotic prescription practices, and facility-level patient caseloads over the months preceding study initiation. The findings will be used to 1) inform the development of the interventions (ZanEMR-AS and the Antibiotic Stewardship Club), 2) generate baseline antibiotic prescription data to support randomization stratification, and 3) provide contextual information to aid interpretation of subsequent trial results. These descriptive analyses are not part of the trial evaluation and will not involve hypothesis testing.

8 STUDY SETTING

The cluster RCT, qualitative, and cost and cost-effectiveness studies will be based in public dispensaries in Unguja island, Zanzibar, Tanzania. The Before-After analysis study will take place in public dispensaries and health centers on both Unguja and Pemba islands of Zanzibar, Tanzania. Zanzibar, a semi-autonomous region of Tanzania has a population of 1,889,773 (2022) with an HIV prevalence of 0.4% (15-64 years)[62], and malaria prevalence of less than 1 %.[63] There are 136 public primary care level health facilities: 90 dispensaries and 46 health centres. A universal health insurance scheme allows residents of Zanzibar to universal access to public healthcare, with no user fees. This includes outpatient consultations, laboratory tests, and treatment provided in primary healthcare facilities. In dispensaries, patients are usually managed by clinical officers, a non-physician clinician with 3 years of education after secondary school,[64] or nurses with 1-3 years of education. ZanEMR, the national EMR system, is currently being deployed in public primary care level health facilities.

9 ELIGIBILITY CRITERIA

9.1 DAWA I and DAWA II Cluster Randomized Controlled Trial

Table 3: Eligibility criteria for DAWA I and DAWA II

Analysis	Level	Inclusion criteria	Exclusion criteria

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Primary analysis	Health Facility	- Government or government designated primary healthcare facilities (dispensaries) open to the general public - Health facilities with the Zanzibar Electronic Medical Record system (ZanEMR) available in consultation rooms.	- Health facilities that are planning to be closed for more than 2 weeks during the conduct of the study
Primary analysis	Patient	- Patients of all ages presenting to participating health facilities for a presumed acute infectious illness (presence of any of the following symptoms or signs for less than 2 weeks: fever, cough, runny nose, sore throat, ear pain, ear discharge, pain urinating, genital complaints, diarrhea, vomiting, skin infection [abscess, pustules]) for their initial consultation related to an acute infectious illness	- Patients presenting for any other acute non-infectious illness-related consultation, including follow-up consultation (planned or unplanned), chronic care consultation, vaccination consultation, or well-child visit consultation - Patient referred from another health facility - Patient already included in the study for a previous consultation
Expanded analysis (DAWA I) and long-term outcome analysis (DAWA II)	Patient	- Patients presenting to participating health facilities for an acute illness (including non-infectious illness-related consultations)	- Patient re-attending health facility (ie. Patients with any «re-attendance» diagnosis) - Patient referred from another health facility

All health facilities on Unguja island, Zanzibar will be assessed for eligibility. If too many health facilities are available, we will take a random sample of 39 facilities. If not enough health facilities are available (e.g. due to insufficient ZanEMR implementation by that time), then we will extend eligibility assessment to include health centres that have similar profiles as dispensaries. Criteria for deciding on which health centres to include will be 1) average number of consultations per month, and 2) total number of health care providers seeing acute illness patients at outpatient. If the number of dispensaries and health centers in Unguja is insufficient, health facilities from Pemba will be sampled as well, prioritizing dispensaries.

The difference in the primary analysis population between DAWA I and DAWA II is due to the absence of research assistants in DAWA II to systematically identify patients with acute infectious illnesses. This decision was made to minimize the Hawthorne effect and was also influenced by logistical and feasibility constraints.

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9.2 Qualitative studies

We will enroll healthcare workers using ZanEMR-AS and/or participating in the Antibiotic Stewardship Club meetings, and stakeholders from the Ministry of Health, Health Management Teams, or any other person directly involved in the project implementation or directly affected by the intervention.

9.3 DAWA III - Before-After Analysis

Table 4: Eligibility criteria for DAWA III

Level	Inclusion criteria	Exclusion criteria
Health Facility	- Government or government designated primary healthcare facilities (dispensaries) open to the general public - A functioning Zanzibar Electronic Medical Record system (ZanEMR) is available in consultation rooms and in use for a minimum of 4 months	- Health facilities that participated in the DAWA I cRCT already using ZanEMR-AS (intervention)
Patient	- Patients presenting to participating health facilities for an acute illness (including non-infectious related illnesses)	- Patient re-attending health facility (ie. Patients with any «re-attendance» diagnosis) - Patient referred from another health facility

10 INTERVENTIONS

10.1 DAWA I and II – Cluster Randomized Trial

The interventions directed at reducing antibiotic prescribing will be inspired by the WHO practical toolkit for Antimicrobial stewardship programs in health-care facilities in low- and middle-income countries and guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America, and in line with National Zanzibar digital health and antimicrobial resistance strategies.[59,60,65,66] To make sure the interventions are well adapted to the setting of implementation, a situational or SWOT analysis will be conducted. This will help determine the needs, while setting realistic expectations on what can be done. To identify the strengths (S), weaknesses (W), opportunities (O), and threats (T), we will observe consultations, and discuss with primary care healthcare providers, public health officials, and patients. The interventions for the DAWA I cRCT will be implemented in health facilities according to allocation arm. Pending further input from end-users and stakeholders, details of each specific intervention follows:

- **Intervention arm 1:**
    - ZanEMR-AS with initial group training and supported mentorship visits
    - Audit and Feedback Benchmarking Dashboards
    - Antibiotic Stewardship Club
- **Intervention arm 2:**
    - ZanEMR-AS with initial group training and supported mentorship visits
    - Audit and Feedback Benchmarking Dashboards
- **Control arm (Usual care):**
    - ZanEMR: Routinely used electronic medical record, as implemented by the MOHZ, without clinical decision support features for antibiotic stewardship
    - Paper and pdf national guidelines including the Zanzibar Standard Treatment Guidelines, international guidelines including IMCI.
    - Routine supervision by district health management teams

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During the second phase of the study (DAWA II), arm 1 will stop attending Antibiotic Stewardship Club meetings, and both arm 1 and 2 will no longer receive visits supported by the study team. However, arm 1 and 2 will continue to access ZanEMR-AS and Audit and Feedback Dashboards.

10.1.1 ZanEMR-AS

ZanEMR-AS is the Zanzibar Electronic Medical Record (EMR) System developed by the Ministry of Health with additional features to encourage antibiotic stewardship. It is a modification to the standard EMR called ZanEMR that will be used in usual care health facilities. The Ministry of Health will conduct the software development of ZanEMR-AS, with input and guidance by the study team and clinical validation by a group of clinical experts. The additional features will be simple clinical decision support features that can be seamlessly integrated into ZanEMR architecture, based on national/international guidelines, and must have the potential to reduce unnecessary or inappropriate antibiotic prescriptions. Their potential for antibiotic stewardship will be balanced against possible negative impact on users' experience. Efforts will be made to minimize workflow disruption, unnecessary clicks, alert fatigue and consultation time.

The algorithm will be developed based on the Zanzibar and Tanzania Standard Treatment Guidelines, the WHO Integrated Management of Childhood Illness (IMCI), the WHO Integrated Management of Adults and Adolescents Illnesses (IMAI), the Practical Approach to Care Kit (PACK) clinical algorithms, WHO AWaRe (Access, Watch, Reserve) antibiotic book, and targeted literature reviews.[67-72] The choice of diagnoses to target for clinical decision support will be informed by the most frequently encountered conditions for which antibiotics are prescribed, identified in the pre-trial descriptive analyses of routine ZanEMR data and relevant literature. The clinical algorithms will be validated by a group of clinical experts from Tanzania and Zanzibar.

An expert review committee, comprising purposely selected specialists and general clinicians working at different levels of care in Zanzibar, will be asked to validate the clinical content of ZanEMR-AS. Discussions will be held during an in-person meeting in Zanzibar, where a number of clinical questions will be discussed and voted on. For each question, the option obtaining a majority of votes will be retained. If deemed necessary by the expert panel, and in the event of difficulties in reaching a consensus, certain questions can be referred to specialist associations (e.g., the Paediatric Association of Tanzania) for a decision. Following this expert meeting, CDSS features will be adapted according to the recommendation. If at a later stage one of the CDSS features needs further modification, the experts' opinion will be sought by e-mail.

Pending input from users and experts, the antibiotic stewardship features may take the following forms:

Diagnosis prompt: This feature will take the form of a pop-up that appears when a certain diagnosis is selected or when specific diagnosis and treatment combinations are selected. The clinical decision support will take the form of a simple set of criteria with checkboxes, a short rule-based algorithm made of 2-3 sets of criteria, or simply provide guidance on what treatment is most appropriate according to different clinical criteria. These features will be developed for diagnoses frequently associated with unnecessary antibiotic prescription in Zanzibar, based on baseline data and a literature review.

Treatment proposal: This feature will involve preselected order sets proposing the appropriate treatment primarily based on the Zanzibar Standard Treatment Guidelines, as well as the WHO AWaRe guidelines. This feature will be primarily developed for diagnoses frequently leading to unnecessary or inappropriate antibiotic prescriptions.

General treatment discordance alert: When an antibiotic is selected in the treatment tab, but none of the selected diagnoses require an antibiotic, an alert will pop-up indicating that the selected antibiotic is not required based on the diagnoses. All ICD-10 diagnoses will be coded and linked to one of 4

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categories (A. antibiotic required, B. antibiotic sometimes required, C. antibiotic rarely required, D. no antibiotic required).

Specific treatment discordance alert: For certain ICD-10 diagnoses that only require antibiotics in specific situations, a specific discordance alert pops-up when an antibiotic is selected and no other diagnoses requiring antibiotics (category A or B above) was selected. The pop-up can take the form of a simple alert, a simple set of criteria with checkboxes, or a short rule-based algorithm to determine whether the patient really needs an antibiotic or not

AWaRe classification of antibiotics: All antibiotics will be classified according to the WHO AWaRe classification. Antibiotics belonging to either the "Reserve" or "Not Recommended" categories from the WHO AWaRe classifications will appear in red when selected in the treatment tab. Antibiotics belonging to the "Watch" category will appear in orange.

In addition to these features, audit and feedback benchmarking dashboards will compare antibiotic prescription rates among health facilities and healthcare providers. Overall prescription rates, as well as prescription by AWaRe categories, and by clinical syndromes will be presented. Dashboards will be shared with healthcare providers from participating health facilities and relevant public health officials including the DHMT. Dashboards will be reviewed and discussed with clinicians during supported mentorship visits in arm 1 and 2, and during antibiotic stewardship clubs in arm 1.

Baseline training and support for routine mentorship visits: At intervention start, a centralized group training will be conducted, to help healthcare workers understand and effectively use the new EMR features. Additionally, 1-2 visits per health facilities will be conducted to provide on-site mentorship. These visits will be conducted together with the respective District Health Management Teams (DHMTs) in Zanzibar, who conduct regular visits to primary health facilities as part of routine supervision. The study team will accompany the DHMTs to provide support related to ZanEMR-AS features, notably the benchmarking dashboards, but the procedure will remain similar to usual visits.

10.1.2 Antibiotic Stewardship Club

This intervention will consist of Antibiotic Stewardship Club meetings, and Antibiotic Stewardship Commitment posters:

Antibiotic Stewardship Club meetings: monthly meetings with healthcare providers will be conducted with 2 facilitators over a period of 6 months (6 meetings in total). 2 healthcare providers from each participating health facility will be invited to the meetings, that will include time for discussions, education, food, and drinks. Upon completion of the stewardship meetings, healthcare providers will receive a certificate to certify their expertise in antibiotic stewardship. The content of the meetings will include:

- **Review of antibiotic prescribing** from the previous month and evolution over time during the club meetings of the participating health facilities utilizing a clear/simple benchmarking dashboard. This dashboard will compare antibiotic prescribing between different health facilities, and compared to a pre-specified optimal antibiotic prescription threshold (Less than 30% as defined by the WHO).
- **Discussion of challenges and opportunities** of rational antibiotic prescribing. Healthcare providers can discuss about different clinical situations for which withholding antibiotics was challenging, and examples of clinical situations where an antibiotic was successfully withheld.
- **Targeted clinical training:** Refresher training on specific syndromes, reviewing when an antibiotic is indicated or not.

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- **Communication training** on methods to explain why antibiotics are not necessary, with opportunities for role play activities between healthcare providers

Antibiotic Stewardship Commitment Posters: In order to valorize the healthcare providers motivation to reduce antibiotic prescribing, Antibiotic Stewardship Commitment Posters will be given to participating healthcare providers so that they can put up in their health facilities. This demonstrates their dedication to antibiotic stewardship principles, and helps hold them accountable to patients. Posters eliciting this commitment have previously shown potential to reduce antibiotic prescription.[73]

10.1.3 Usual care (control arm)

Health facilities randomized to usual care will provide care as per usual. Healthcare providers would use ZanEMR to enter clinical data, diagnoses, treatment and referral strategy, but no antibiotic stewardship features from ZanEMR-AS will be included. The implementation of ZanEMR will/was done independently from the study by the Zanzibar Ministry of Health. Guidelines available to guide antibiotic prescribing among healthcare providers include the Zanzibar Standard Treatment Guidelines and IMCI.

10.2 DAWA III - Before-After Analysis Interventions

- Before: Usual care (control)
- After: ZanEMR-AS with adaptations based on the DAWA I – cluster randomized trial, baseline training, and supported mentorship visits.

11 OUTCOMES / ENDPOINTS

11.1 DAWA I and II – Cluster Randomized Trial:

The primary outcome is the proportion of encounters with an antibiotic prescribed at day 0 among patients enrolled in the study with a suspected infectious illness, measured during months 3, 4 and 5 after the initiation of the interventions (Baseline month 0). The outcome aligns with the WHO/International Network of Rational Use of Drugs (INRUD) core prescribing indicators.[74] This outcome was selected given the high rate of antibiotic prescribing in primary healthcare facilities and its associated consequences, including adverse drug reactions, increased healthcare costs, microbiome disruption, and the development of bacterial antimicrobial resistance. The outcome is limited to patients visiting participating health facilities 3 to 6 months after the intervention begins (ie. During month 3 to 5), as it is hypothesized that the intervention requires at least 3 months to take effect and that the required sample size at each facility can be enrolled within 2-3 months. Antibiotic prescription on day 0 was chosen rather than at day 7 due to challenges in reliably determining whether patients received additional antibiotics after the initial consultation—particularly because patients and caregivers often cannot accurately identify whether the medications provided were antibiotics.

Table 5: Primary and Secondary Outcome Definitions

Outcome	Definition	Time point	Means of assessment

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Primary Outcome			
Antibiotic prescription	Proportion of encounters with an antibiotic prescribed	At day 0 (day of presentation)	ZanEMR or ZanEMR-AS as documented by the clinician or eCRF if ZanEMR or ZanEMR-AS is not functionning
Secondary Outcomes: Harms outcomes			
Clinical status worse	Proportion of patient encounters for which patients report they are worse compared to baseline (day 0) consultation	At day 7	Phone call at day 7 (range 7-8)
Severe adverse outcome (composite outcome combining: 1) hospitalization without referral, and 2) dead by day 7	Severe adverse outcome: Proportion of patient encounters for which the patient is 1)Hospitalized without referral[a] OR 2) Dead: Patients reported dead by day 7	By day 7	Phone call at day 7 (range 7-8)
Unplanned follow-up consultation	Proportion of patient encounters for which a patient presents to a health facility for an unplanned follow-up consultation	By day 7	Phone call at day 7 (range 7-8)
Secondary Outcomes: Antibiotic Stewardship			
Additional medications	Proportion of patient encounters for which the patient uses additional medications not prescribed by healthcare provider at the initial encounter	By day 7	Phone call at day 7 (range 7-8)
Diagnostic-concordant antibiotic prescribing	Proportion of patient encounters in which an antibiotic was prescribed when clinically indicated based on the diagnosis, or not prescribed when not indicated[b] (regardless of antibiotic class, dosage or administration route)	At day 0	ZanEMR or ZanEMR-AS as documented by the clinician or eCRF if ZanEMR or ZanEMR-AS is not functionning

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Antibiotics categorized as an "Access" antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended)	Proportion of patient encounters prescribed an "Access" antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended) among all encounters prescribed an antibiotic	At day 0	ZanEMR or ZanEMR-AS as documented by the clinician or eCRF if ZanEMR or ZanEMR-AS is not functionning
Exploratory Outcome: Extended population			
Antibiotic prescription in all patients	Proportion of patient encounters prescribed an antibiotic in all patients (not limited to those with a presumed infectious illness)	At day 0	ZanEMR or ZanEMR-AS as documented by the clinician
Antibiotic prescription in patients over the whole implementation period	Proportion of encounters prescribed an antibiotic in patients with a presumed infectious illness, and during the whole implementation period (month 0-5)	At day 0	ZanEMR or ZanEMR-AS as documented by the clinician
Know-do gap in terms of appropriate antibiotic prescription in all patients over the whole implementation period	Proportion of encounters with or without appropriate antibiotic prescription in comparison to knowledge on what is considered appropriate according to diagnosis[b].	At day 0	ZanEMR or ZanEMR-AS as documented by the clinician AND Baseline survey of healthcare providers on appropriateness of antibiotic prescription for specific diagnoses[b]
Long term outcomes: DAWA II			
Long term antibiotic prescription	Proportion of encounters presenting for an acute illness with an antibiotic prescribed at day 0	At day 0 (during month 6 to 11)	ZanEMR or ZanEMR-AS

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Diagnostic-concordant antibiotic prescribing	Proportion of patient encounters in which an antibiotic was prescribed when clinically indicated based on the diagnosis, or not prescribed when not indicated[b] (regardless of antibiotic class, dosage or administration route)	At day 0 (during month 6 to 11)	ZanEMR or ZanEMR-AS
Antibiotics categorized as an "Access" antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended)	Proportion of patient encounters prescribed an "Access" antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended) among all encounters prescribed an antibiotic	At day 0 (during month 6 to 11)	ZanEMR or ZanEMR-AS
Trend in antibiotic prescription over whole study period (exploratory)	Evolution over time of the proportion of encounters presenting for an acute illness with an antibiotic prescribed	At day 0 (during month 0 to 11)	ZanEMR or ZanEMR-AS

[a]Hospitalization without referral by a health provider at the baseline consultation

[b]Appropriate antibiotic prescription based on pre-specified matching of ICD-10 diagnoses requiring antibiotics based on national guidelines (and international guidelines if not clear in national guidelines)

11.2 DAWA III – Before-After Analysis

The DAWA III Before-After analysis will use the same primary outcome as the DAWA I cluster RCT however will include all patients presenting for an acute illness, not only those presenting with a presumed infectious illness: "Proportion of encounters presenting for an acute illness with an antibiotic prescribed at day 0."

Secondary outcomes using the same outcome definitions as the DAWA I cluster RCT, include

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1) Diagnostic-concordant antibiotic prescribing at day 0, and

2) Proportion of encounters prescribed an "Access" antibiotic according to the WHO AWARE classification (Access, Watch, Reserve, Not recommended).

All outcome data will be be retrieved from ZanEMR or ZanEMR-AS as documented by the clinician.

11.3 Qualitative evaluation

Qualitative studies will explore healthcare providers and stakeholder perception of intervention, its feasibility and acceptability, as well as barriers and facilitators for rational antibiotic prescribing by healthcare providers.

12 STUDY PROCEDURES

The health facility schedule, implementation and assessment is summarized in table 6. Data collection for the cluster randomized trial is expected to start in October 2026 (M0) and end in September 2027 (M11), while the DAWA III Before-After will analyze available data up until November 2027, with implementation of ZanEMR-AS in new facilities starting April 2027.

Table 6: DAWA I and DAWA II Health facility schedule of enrolment, implementation, and assessment

	Pre-implementation	Study implementation (DAWA I)						Post-study evaluation (DAWA II)
Time point (Month)	M -12 to -1	M0	M1	M2	M3	M4	M5	M6 to M11
Health Facility Enrolment	x							
Eligibility screening	x							
Randomization	x							
Implementation		x	x	x	x	x	x	
ZanEMR-AS centralized training	x							
Intervention arm 1 Zan-EMR AS		x	x	x	x	x	x	x
Intervention arm 1 Antibiotic Stewardship Club		x	x	x	x	x	x	
Intervention arm 2 ZanEMR-AS		x	x	x	x	x	x	x
Control arm – Usual care (ZanEMR)		x	x	x	x	x	x	x
Study data collection		x	x	x	x	x	x	x
DAWA I Cluster RCT primary outcome data collection					x	x	x	
DAWA I Cluster RCT longitudinal outcome data collection[1]		x	x	x	x	x	x	

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DAWA II Cluster RCT long-term outcome study								x
Qualitative studies		x	x	x	x	x	x	

[1]Corresponds to the exploratory outcome: Proportion of encounters prescribed an antibiotic in patients with a presumed infectious illness, and during the whole implementation period (month 0-5)

12.1 DAWA I and II cluster randomized trial

All health facilities on Unguja island, Zanzibar will be assessed for eligibility. Implementation of the interventions will start 3 months before official start of study enrollment in health facilities. Starting month 3, following baseline implementation (month 0), research assistants will screen and recruit participants in the waiting area prior to consultation. Research assistants will collect participant name, phone, date of birth, sex, and primary reason for attendance. In the case of children, the name and role of caregiver will also be collected. If the patient or caregiver does not have a phone, the phone number of a close relative or friend will be requested. The clinical consultation will be conducted by routine healthcare providers of the health facilities. If ZanEMR or ZanEMR-AS is functioning, healthcare providers in all arms will enter clinical data in ZanEMR/ZanEMR-AS. If the EMR is not functioning, consultations will be documented by routine healthcare providers on paper logs, as per usual guidance. After the consultations, research assistants will collect data on the diagnoses and treatments prescribed for each enrolled patient when the EMR is not functioning. Research assistants will ask for clarifications if the written diagnoses and treatments are not clear.

7 days after the consultations, patients/caregivers who provided their phone number will be contacted to assess clinical outcome, and treatment and health seeking use/behaviour. If the patient is not reachable, at least 3 other attempts will be attempted at different times, and up to 3 days after. In case a patient reports no clinical improvement, or new or worsening symptoms, they will be advised to seek medical care at the nearest health facility. The study flow diagram is found in figure 1.

6 months after study implementation, the DAWA II phase starts, in which the antibiotic stewardship club meetings and supported mentorship visits will have finished. Research assistants will no longer enroll patients, and data will be collected as per routine procedures within ZanEMR or ZanEMR-AS for 6 months.

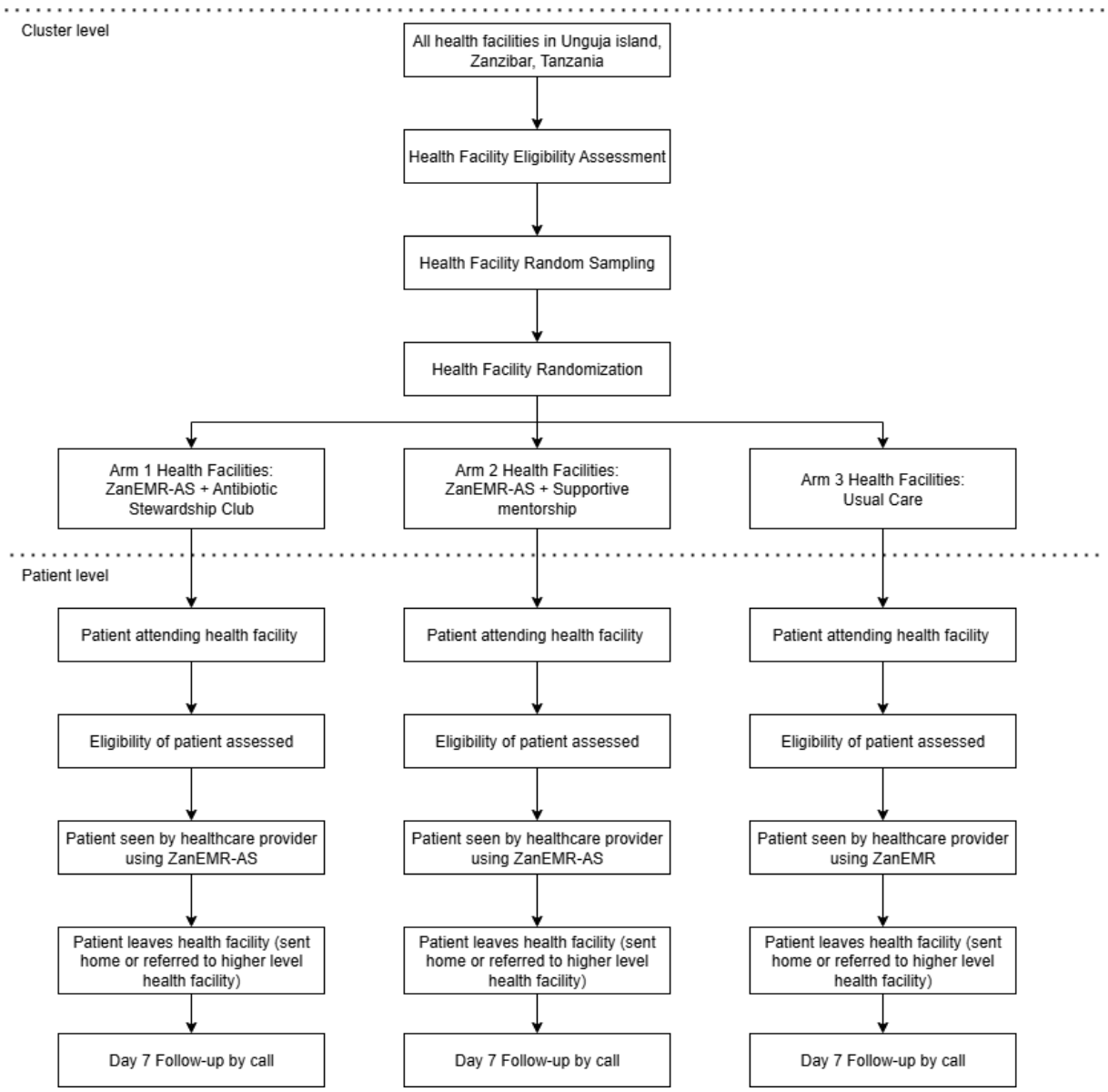
Discontinuation of study sites

To preserve the pragmatic nature of the study, no predefined criteria for discontinuation of study sites will be applied throughout the study period, including in situations where the intervention cannot be implemented as planned. In case ZanEMR is discontinued from an included health facility, it will still remain included for the primary ITT analysis, unless data collection is no longer feasible.

Since the intervention is delivered at the health facility level, no discontinuation criteria will apply to patients.

Figure 1. Study procedures diagram of the DAWA I cluster randomized trial

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13 SAMPLE SIZE

13.1 DAWA I – Cluster Randomized Trial

The DAWA I cluster RCT sample size was calculated to demonstrate a minimum absolute antibiotic prescription proportion reduction of 25% in the two pairwise comparisons of each intervention arm compared to the control arm. We assumed a baseline antibiotic prescription of 75%,[33,75,76] and an Intraclass Correlation Coefficient (ICC) of 0.2,[36] and a Coefficient of Variation (CV) of 0.1. Using an alpha of 0.05, a power of 80% and controlling for equal cluster sizes, we would require 13 clusters per arm and at least 40 participants per cluster. Based on current data of the involved health facilities, we can

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expect approximately 33% of patients presenting with an acute infectious illness to be under the age of 5. To have a sufficient sample size for the under 5-year-old age group (a priori key subgroup analysis), while keeping the overall patient case-mix to infer to the general population, we increased the sample size to 150 participants per cluster. This will also enable better inference on the key secondary endpoints at day 7, where we expect loss to follow-up of up to 30%.[36] Given that the Antibiotic Stewardship Club intervention is expected to have a full impact only after 3-4 months of the implementation and it will only take 2-3 months to enroll a random sample of 150 patients per cluster, our primary analysis population who will be followed up for all endpoints will be enrolled at month 3 to 5 after the start of implementation. This results in a total sample size of 1,950 patients per arm, for a total of 5,850 patients.

Sample size calculations are available online: https://rpubs.com/AlainAmstutz/dawa.

13.2 Qualitative study

The final sample size for qualitative studies will be determined by data saturation (when new data no longer produces new themes or ideas). It is estimated that about 13-17 in-depths interviews will be necessary to reach data saturation (about 10 with healthcare providers, and 5 with stakeholders from the Ministry of Health and Health Management Teams). For the non-participant observations, data collection will occur during 6 to 12 of the antibiotic stewardship club meetings

13.3 DAWA III - Before-After Analysis

The formal sample size for this study will be calculated at a later time when more information is available. Nonetheless, considering the sample size calculated for the cluster-randomized trial, we expect to have sufficient power to perform this analysis as we expect to be able to include more than 30 health facilities, at least 4 months of pre-intervention data, and 4 months of post-intervention data, with on average 400 consultations per month per facility.

14 RECRUITMENT

14.1 DAWA I - Cluster Randomized Trial

14.1.1 Cluster level

Cluster (health facility) recruitment will occur 1-4 months prior to the start of implementation. Consent to participate in the study will be sought from the ministry of health of Zanzibar, through the Directorate of Preventive Services and health Education (DPSHE), the District Medical Officers and the respective health facility in-charge before randomization.

14.1.2 Individual level

It is estimated that patient recruitment will last 2 to 3 months to reach sample size. Recruitment will start at month 3 after baseline (month 0), up to month 4. If the sample size is not reached in a health facility by month 4, the recruitment period will be extended up to month 5.

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Patients will be recruited in-person at participating health facilities. After a patient is registered at the health facility for an acute illness outpatient consultation, a research assistant will approach patients to be screened for eligibility and collect verbal consent. In health facilities where registration is conducted by the clinician in the consultation room, research assistants will screen patients in the waiting areas to be seen by healthcare providers providing the acute illness outpatient consultations. Given the different particularities of health facilities the exact location of recruitment will differ to ensure patient confidentiality, and to maximize recruitment of eligible participants.

To minimize variation in cluster sizes due to different attendance rates across dispensaries, a differential enrollment schedule will be implemented. In low attendance dispensaries, enrollment will occur daily. With an estimated 150-250 consultations per month in low attendance dispensaries, for which an estimated 60% are first time consultations for an acute infectious illness, such health facilities will likely enroll the required sample size per health facility (150) in 1.5 - 2 months. In contrast, in high attendance health facilities, patients will be enrolled on randomly selected days, approximately every other day, to limit excessive recruitment from these facilities compared to others, and in order to have similar enrolment timelines. On enrollment days, all eligible patients screened will be enrolled, to avoid selection bias. The enrollment schedule will be pre-determined based on observed attendance rates in the pilot phase and first months of intervention (month 0-2). If imbalance between clusters is still large, the enrollment schedule will be adapted accordingly, adding or removing enrollment days where necessary.

For the expanded population in the DAWA I phase and for long-term outcomes in the DAWA II phase, no direct patient recruitment will take place, as analyses will rely exclusively on routinely collected data.

14.2 Qualitative studies

Participants will be recruited for semi-structured in-depth interviews by purposive sample, among healthcare providers who are exposed to the intervention during the DAWA I study. Healthcare providers from varying background and characteristics will be selected (eg. nurses vs clinical officers, working in rural or urban area, male and female). Information on the study will be provided to potential participants at least one day prior to the interview, and their written consent collected on the day of the interview (see informed consent forms in Annex: A09 to A12).

For the non-participant observations, all healthcare providers attending the antibiotic stewardship clubs will be invited to participate. Depending on attendance to antibiotic stewardship clubs, the participants can change from one month to the next. Information on the study will be provided to potential participants at least one day prior to the observations, and their written consent collected on the day of the observation (see informed consent form in Annex: A13, A14). In case one or more healthcare provider attending the antibiotic stewardship clubs does not wish to participate, what they say or do will not be written down by the observer, and will not be transcribed from the audio record.

14.3 DAWA III – Before-After Analysis

14.3.1 Cluster level

Cluster recruitment will occur according to the implementation schedule determined by the Ministry of Health. As the rollout schedule will be determined by the health authorities of Zanzibar, the

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research team will identify and invite eligible facilities for participation only once they are selected to receive the intervention. Thus, timing of recruitment will likely vary across facilities.

14.3.2 Individual level

No direct patient recruitment will occur, since the study will use routinely collected coded data.

15 ALLOCATION: DAWA I AND II – CLUSTER RANDOMIZED TRIAL

15.1 Sampling

A random sample of dispensaries will be selected among eligible health facilities by an independent statistician using Stata or R. If at the time of sampling there are not enough eligible heath facilities, the inclusion criteria will be modified to include other eligibility criteria (see section 9.1 eligibility criteria).

15.2 Sequence generation

The allocation sequence for health facilities included in the DAWA I and DAWA II Cluster Randomized Trials will be generated by an independent statistician, not involved in the implementation of the study, using computer-generated randomization using Stata or R. Health facilities will be randomized 1:1 stratified by baseline antibiotic prescription and attendance rates using covariate-constrained randomization. In case health facilities from Pemba have to be included due to insufficient eligible health facilities in Unguja, geographical location (Pemba vs Unguja) will be added as a stratification factor.

No allocation sequence will be necessary at patient level, since patients will be allocated to the intervention based on the facility they attend.

15.3 Allocation concealment and implementation

Health facilities will be enrolled into the trial by the study team, who will be unaware of the allocation sequence prior to enrollment. The assigned intervention arms will be communicated by the study statistician to study implementers only after health facilities are confirmed for inclusion.

15.4 Blinding

Due to the nature of the intervention, healthcare providers cannot be blinded to the intervention. However, patients, research assistants enrolling patients and assessing primary outcome, as well as research assistants assessing D7 outcomes by phone call will remain blinded to the intervention allocation, to the extent possible.

ZanEMR-AS is indistinguishable from the routinely used ZanEMR without connecting with a clinician login and entering consultation data, preventing patients and research assistant to know which version is used and thus which study arm their health facility is part of. They may however notice antibiotic stewardship commitment posters in health facilities randomized to receiving the antibiotic stewardship club meetings, however there would be no indication that this poster is part of the study intervention. Healthcare providers will be instructed not to disclose intervention allocation to research assistants and patients. In case accidental unblinding occurs, no participants or research assistant will be excluded.

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16 DATA COLLECTION, MANAGEMENT AND MONITORING

16.1 Data collection methods

16.1.1 DAWA I – Cluster Randomized Trial

Data will be obtained via three different methods: collected by research assistants at health facilities, via phone call for follow-up, and via ZanEMR. In addition, baseline surveys of all participating healthcare providers (in all study arms) will be conducted at different points during the study implementation to determine their knowledge on appropriateness of antibiotic treatment for 5-10 diagnoses at baseline.

Research Assistants at health facilities:

All data collected by research assistants at health facilities will be collected in a REDCap eCRF hosted in Tanzania at the Ifakara Health Institute (See annex A01).[77] Research assistants will screen patients and record inclusion criteria in the eCRF. For enrolled patients, identification data including name, date of birth, sex and contact information for follow-up will be collected. In case the EMR is not functioning, research assistants will review paper logs used by clinicians and document the diagnosis and prescribed treatment.

Research assistants based in health facilities will be trained to collect data, including some supervised screening and data collection sessions in health facilities with a study clinical coordinator prior official enrollment start.

Phone calls at day 7

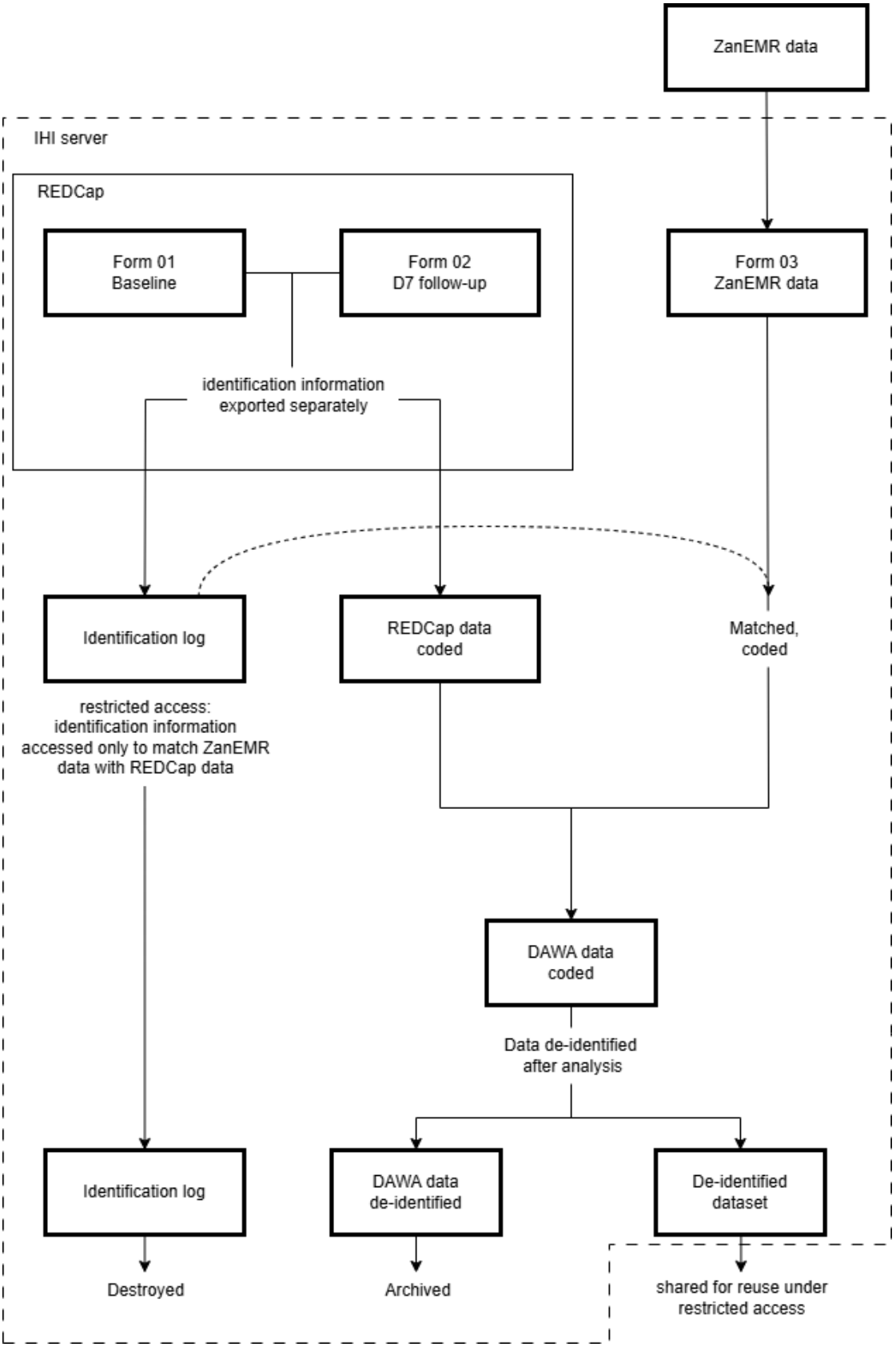
Day-7 outcomes will be obtained by phone call to patients or their caregivers performed by separate research assistants, and documented in a REDCap eCRF (see Annex A02). To ensure data quality and standardize data collection, data collection guides with simple, closed-ended questions will be provided to research assistants. Research assistants performing phone calls will be trained prior study start, including test phone calls, and the provision of standardized phone call scripts to ensure effective communication. The first phone calls will be supervised by one of the study clinical coordinators. If the patient is not reachable, at least 3 other attempts will be attempted at different times of the day, and up to 3 days after the scheduled follow-up date. Due to logistical and resource constraints no home visits will be undertaken. While home visits could potentially increase follow-up rates, they would introduce additional sources of bias (ex. Selectively capturing only patients who are at home during daytime hours) and substantially increase operational complexity. We therefore chose a standardized, phone-based follow-up strategy that is feasible, minimizes differential bias, and ensures equity across participants.

ZanEMR data:

When ZanEMR is functioning, the diagnosis and treatment for our primary population, as well as all data concerning the expanded population (patients with any acute illness) and the long term outcomes of the DAWA II phase, will be obtained through ZanEMR, or ZanEMR-AS. Data collected via the EMR include names, date of birth, ZanEMR ID, demographics, type of consultation, vital signs, chief complaint, history of present illness, provisional diagnoses, investigations, confirmed diagnosis, treatment, and referral strategy (see Annex A03 form 03). This data is routinely entered in the EMR by health facilities' admin staff, nurses and clinicians.

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Figure 2: data management diagram



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16.1.2 Qualitative studies

Interview guides for in depth interviews and observation checklist are provided in Appendix A04 to A08. They were developed using the Consolidated Framework for Implementation Research (CFIR).[78] In depths interviews and antibiotic stewardship clubs will be audio recorded, transcribed and translated into English.

16.1.3 Cost and cost-effectiveness

All clinical data will be obtained through ZanEMR or ZanEMR-AS, including costs related to treatment prescriptions. Costs related to the Antibiotic Stewardship Club meetings, supported mentorship visits and training will be collected as per routine expense documentation and visit logs.

16.1.4 DAWA III - Before-After analysis

All data will be obtained through ZanEMR or ZanEMR-AS.

16.1.5 Pre-trial Descriptive Analyses of ZanEMR

Routine ZanEMR data from the pre-trial period will be extracted in de-identified form for descriptive analyses.

16.2 Data management and confidentiality

16.2.1 DAWA I and II

Data entry and coding: field restrictions and data definitions in the eCRFs will minimize entry errors. Compulsory data entry fields will prevent missing values. Standard Operating Procedures for data collection will be developed to guide research assistants and ensure rigorous data collection.

For data obtained through the EMR, variables such as diagnoses are selected by clinicians from a list of ICD10 diagnoses, and treatments are selected from a predefined list. Documenting diagnosis and treatment in the EMR is compulsory, as it is required for dispensing medications at the health facility pharmacy.

Security and storage:

During the project, the data files will be managed and stored on an Ifakara Health Institute server in Tanzania that holds an ISO 27005 norm, with daily backups. The server offers good protection for the data (integrity and confidentiality) and is resistant to failures and hardware and software-related problems. Access to this data will be restricted using two-factor authentication by investigators. Access to each dataset will be restricted to the investigators directly involved in each study. When exporting REDCap data for analysis, identification data will be exported in a separate file and kept under restricted access (Figure 2). It will only be accessible to research assistants performing follow-up at day 7, and investigators when matching REDCap data with ZanEMR data.

During the data cleaning process, data collected via REDCap and ZanEMR will be matched, merged, and coded (names replaced by study ID, ZanEMR ID deleted). For the analysis, coded data will be shared to a secured Unisanté server, to be made accessible exclusively to DAWA investigators based in Switzerland.

Once analysis complete, the identification log will be destroyed, and the DAWA data will be de-identified and archived on an IHI secure server.

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At the same time, for public data sharing, a de-identified version of the data will be made available upon request through a secure data repository. Open Access data are not possible, as a re-identification risk remains. An evaluation will be performed at the end of the project by a documentation and data unit team, to evaluate if a subset of the data could be fully anonymized and shared in Open Access.

16.2.2 DAWA III

The same procedure will be followed as for DAWA I, except no data will be collected via RedCap.

16.2.3 Qualitative studies

A similar procedure will be followed as for DAWA I. Once transcribed, the audio records will be deleted. Transcripts will be coded, and participants names and identifying information stored separately. Once analyzed, the data will be de-identified and archived. A de-identified dataset will be made available upon request through a secure repository and shared for research purposes only.

16.3 Data monitoring

No data safety monitoring board (DSMB) is planned for the conduct of these studies, as the studies are considered low risk (intervention is only guideline-implementation: education, audit/feedback, EMR prompts), and no interim analyses are planned.[79]

17 ANALYSIS / STATISTICAL METHODS

17.1 DAWA I and II – Cluster Randomized Trial

The primary analysis of this three-arm cluster RCT will be two independent pair-wise comparisons:

- Pairwise comparison 1: Intervention 1 (ZanEMR-AS + Audit and feedback benchmarking dashboard + Routine mentorship support + Antibiotic Stewardship Club) versus usual care (control), and
- Pairwise comparison 2: Intervention 2 (ZanEMR-AS + Audit and feedback benchmarking dashboard + Routine mentorship support) versus usual care (control)

Both comparisons will follow the same analysis approach outlined below.

We define the primary analysis of the primary and secondary outcomes as follows:

1) It will follow the intention-to-treat principle, (i.e. regardless if the intervention was interacted with or not, regardless if healthcare providers attended antibiotic stewardship meetings, etc)
2) It will be conducted in the primary analysis population: Patients of all ages presenting to a participating health facility for an acute infectious illness
3) Due to the relatively low number of clusters in each comparison (n=<30), we use a generalized linear mixed model (GLMM) with restricted pseudo-likelihood estimation and small-sample correction for degrees of freedom (clusters minus cluster-level parameters), as suggested by Thompson and colleagues.[80] This analysis approach offers unbiased effects for binary outcome analyses across a wide range of scenarios, greater or competitive power compared to generalized estimating equations with sandwich standard errors or cluster-level analysis, greater flexibility in terms of subgroup analyses – and can target both a cluster-average as well as participant-average estimand in case of no cluster size variation (as in our case). This model accounts for clustering by direct modelling of the correlation of the observations in the same clusters using a random effect for clusters. Details about the model as well as its

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implementation in R code are available on: https://rpubs.com/AlainAmstutz/dawa (chapter 2.5.2)

4) We will adjust the model for these *a priori* defined covariates (as fixed effects):
    a. Minimization/Stratification variables: attendance rate, baseline antibiotic prescription rate (as continuous covariates assuming linearity) and pending health facility availability the geographical location (Pemba island vs Unguja island)
    b. Individual-level covariates: Self-reported sex (as binary covariate: male, female) and age (as continuous covariates assuming non-linear association modelled using restricted cubic splines with 3 knots at 10th, 50th and 90th percentiles of the observed age distribution).
    c. Further description of adjustment covariates will be described in the SAP
5) We will report the resulting treatment-effect (beta-1), which is the log-odds difference between intervention and control or – when exponentiated – the adjusted odds ratio, with its 95% confidence interval. This represents a relative cluster-specific effect, conditional on all included covariates. In addition, we will use marginal standardization and report the resulting population-average marginal relative risk and risk difference with their 95% confidence intervals.
6) We use a complete case analysis (see missing data below)
7) Our hypotheses for the primary outcome are that the intervention 1, or the intervention 2, or both would have a reduced rate of antibiotic prescribing, as compared with usual care. The two comparisons are conducted in parallel – like separate trials – assessing two distinct interventions. The interpretation of the results of one comparison ordinarily has no direct bearing on the interpretation of the other. Many trialists/methodologists argue that multiplicity adjustments are not necessary in such instances because such adjustments would not be necessary if the interventions were compared in separate trials.[81-84] Moreover, this pragmatic trial is not intended for regulatory purposes. Hence, we are not planning any multiplicity adjustment.
8) The intra-cluster correlation coefficient will be reported for all primary and secondary analyses

17.1.1 Sensitivity analyses

We will conduct a naïve per protocol analysis for the primary and harm outcomes. The per protocol analysis will exclude participant-encounters for which the ZanEMR-AS was not used (intervention 1 and 2) or ZanEMR in the usual care arm.

17.1.2 Subgroup analyses

We pre-specified the following **key subgroup analysis**, with a statistical power of 80% (see sample size chapter):

1) Subgroup of children under 5 years of age. Since we have sufficient a priori power for this key subgroup, we consider this analysis as hypothesis testing, not hypothesis generating (exploratory).[85] We use the same analysis approach as for the primary analysis, again among both comparisons. Analyses will be performed for the primary outcome and the key harm outcomes.

We pre-specified four exploratory (hypothesis generating) subgroup analyses. All of them will be analyzed on the primary endpoint using the primary analysis approach, but adding an interaction term to the treatment group. The first 3 are categorical and individual-level covariates, while the fourth is a

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cluster-level covariate and included as a continuous covariate assuming linearity. If the interaction p-value is <0.10, we will continue with within-subgroup analyses and hypothesis testing. We present a descriptive forestplot summarizing all subgroup analyses. This approach aligns with the ICEMAN guidance, recognizing the exploratory nature of subgroup analyses and the limited power to detect heterogeneity.[86] The four exploratory subgroup analyses are the following:

1) Patient age beyond 5 years old: aged 5 to <15 years old vs aged >=15 years old
2) Self-reported sex (male vs female)
3) Patients with acute respiratory infectious illness vs other acute infectious illness
4) Health facility attendance rate (average number of patients seen per week)

17.1.3 Exploratory analyses

The following exploratory analyses will be conducted (details in the statistical analysis plan):

1) Proportion of patient-encounters prescribed an antibiotic at day 0 in all patients presenting for an acute illness (secondary analysis population), not just with a presumed infectious illness
2) Antibiotic prescription trend over the entire intervention implementation period, among all patients first time presenting for an acute illness (secondary analysis population).
3) If both comparisons in the primary analysis result in significant differences compared to usual care (control), intervention 1 will be compared to intervention 2, acknowledging limited power.
4) We will investigate if our primary analysis estimate is affected by informative cluster size by using alternative analysis models such as independence estimating equations[87]
5) We will use multiple imputation by chained equation technique for missing outcome data for the day 7 harm secondary outcomes
6) Modified per protocol analysis for the primary outcome comparing usual care (including only patient encounters documented in ZanEMR compared to intervention arm 1 including all patient-encounters where ZanEMR-AS was used and including only health facilities where at least 50% of Antibiotic Stewardship Club meetings were attended by a healthcare provider from that health facility.
7) Multiple imputation for outcomes relying on day 7 data (see missing data section below)
8) Know-do gap: Knowledge on appropriateness of antibiotic prescription according to 5-10 pre-specified diagnoses will be compared to actual antibiotic prescribing for those same diagnoses to determine the know-do gap in appropriate antibiotic prescribing. Evolution of the know-do gap will be explored over the 6 months of implementation and comparisons between study arms will be explored.

17.1.4 Missing data

The extent and patterns of missing data will be reported transparently. Several types of missing data are possible:

1) **Consultation diagnosis and treatment data**: This is the data source for the primary outcome antibiotic prescription data, as well as some antibiotic stewardship secondary outcomes. This data is expected to be nearly complete, as all healthcare providers are required to document diagnoses and treatments in the EMR or, when unavailable, on paper records. The primary data source will be the EMR, with research assistants recording handwritten diagnoses and treatments during EMR downtime (e.g., electricity outages). We therefore anticipate only a small proportion of consultations with missing diagnosis or treatment data. When such data are missing, this is expected to be missing completely at random (MCAR), reflecting gaps in data capture by research assistants rather than systematic differences in patient care. As such multiple imputation for the primary outcome will not be conducted.

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2) **Baseline covariates for model adjustment:** Given the format of the eCRF used to collect baseline characteristics of enrolled patients, we do not anticipate missing data for variables used to adjust the analysis models. In the event that data is missing, it will be considered as missing completely at random.
3) **Day 7 follow-up outcomes**: Missing data from day 7 outcomes will primarily arise from loss to follow-up. Based on similar studies,[36] we anticipate a substantial proportion of consultations with missing day-7 data. We consider this missingness likely to be missing at random (MAR). To assess this assumption, we will compare baseline characteristics between consultations with and without complete day 7 outcome data using simple chi-square and t-test statistics. Sensitivity analyses will be conducted for secondary harm and antibiotic stewardship outcomes that rely on day 7 follow-up data. Theses analyses will include multiple imputation using chained equation technique incorporating the same a priori-defined baseline covariates used as adjustment factors in the primary models.

Details of all analyses will be prespecified in a dedicated statistical analysis plan

17.2 DAWA II phase – Long-term Outcomes

The same analysis approach will be used for the long-term outcomes, notably using a GLMM with restricted pseudo-likelihood estimation and small-sample correction for degrees of freedom on the complete case ITT population. Given the absence of research assistants during this study, the model will not be adjusted for chief complaints, and no adjustment of baseline antibiotic prescription will be used given that this study aims to evaluate the long-term effect of the previous 6 months of intervention. An exploratory per protocol analysis will also be performed to evaluate the effect of the antibiotic stewardship club meetings at its full potential, including only patient-encounters of healthcare providers who attended at least 3 Antibiotic Stewardship Club meetings.

17.3 Qualitative studies

Data will be transcribed verbatim and translated from local language (Swahili) to English. We will use the framework method for analysis of qualitative data.[88] A random sample of transcripts and translations will be quality checked by listening to audio-recordings and back translations. After familiarization with the data, a first researcher will code a random sample of the interviews/observations, using a qualitative coding software. A second researcher will code the same data sample independently, for inter- rater reliability check. Differences in coding will be discussed and a joint finalized code tree developed, which will be used to code the entire material. We will use both inductive approach (ideas emanating from the data itself) and deductive approach (theoretical understanding, literature review and researcher's experience) for data analysis. By conducting inductive coding, we will ensure that unexpected insights, context-specific challenges, and emerging themes are presented.

17.4 DAWA III - Before-After analysis

Details for this analysis will be outlined in a separate statistical analysis plan.

17.5 Pre-trial Descriptive Analyses of Routine ZanEMR Data

Pre-trial descriptive analyses, described in Section 7.6, will be limited to summary statistics and will not involve hypothesis testing.

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18 ETHICS

18.1 Ethical conduct of the study

The project will adhere to the TRUST Global Code of Conduct for Equitable Research Partnerships, which provides guidance to promote fairness, respect, care, and honesty in collaborations.[89] The study will also be conducted in accordance with the principles of the Declaration of Helsinki,[90] the International Council for Harmonisation – Good Clinical Practice (ICH-GCP) guidelines,[91] the 2016 Council for International Organizations of Medical Sciences (CIOMS) / WHO International Ethical Guidelines for Health-related Research Involving Humans,[92] the National Guidelines on Ethics for Health Research in Tanzania,[93] and all applicable national laws and regulations in Zanzibar and Tanzania. All investigators and study staff will receive training in GCP and local ethical requirements before study initiation.

The study will ensure equitable partnership with local institutions, capacity strengthening, and transparent sharing of results.

18.2 Research ethics approval

The protocol will be submitted to the following research ethics committees / institutional review boards (IRB):

- Ifakara Health Institute IRB, Tanzania
- Office of the second vice president of Zanzibar
- Zanzibar Health Research Institute (ZAHRI), Tanzania
- Cantonal Ethics Review Board of Vaud, Switzerland

18.3 Regulatory status of the ZanEMR-AS intervention

ZanEMR-AS is a type of clinical decision support system that provides prompts and alerts to guide clinicians based on established clinical guidelines with validation from a local clinical expert committee. As such it merely supports the implementation, and strengthens the adherence to clinical guidelines. The intervention does therefore not meet the definition of a medical device and thus regarded as a non-regulated device.

18.4 Protocol amendments

Important protocol modifications will be discussed with all investigators, shared with the national advisory committee, and thereafter submitted to all relevant research ethics committees and trial registries. Minor protocol modifications will be shared with investigators, and submitted to relevant research committees and trial registries if relevant.

18.5 Consent or assent

Consent to implement the intervention (ZanEMR-AS and training meetings for healthcare providers) and to access ZanEMR clinical data from participating health facilities will be sought from the Zanzibar Ministry of Health, through the Directorate of Preventive Services and health Education (DPSHE), the District Medical Officers and the respective health facility in-charge before study randomization. This includes ZanEMR data before implementation of the study to calculate baseline antibiotic prescription used for randomization, and to inform development of clinical decision support features within ZanEMR-AS. Consent from village leaders will be sought through the District Medical Officers and respective health facility in-charge.

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18.5.1 DAWA I and II - Cluster RCT

In accordance with the 2016 CIOMS International Guidance for Health-related Research Involving Humans,[92] and the National Guidelines on Ethics for Health Research in Tanzania,[93] we request:

- Waiver for informed consent for routine day 0 data
- Waiver of *written* informed consent for day 7 data, while providing *structured oral informed consent* supported by a patient information leaflet (Appendix A17 and A18).

This request is in line with the WHO/CIOMS Guideline 10 for which waiver or alteration of consent may be granted when all of the following conditions are met: 1) The research involves no more than minimal risk, 2) it has important social value, and 3) obtaining written consent is impracticable or would compromise scientific validity.

Below is an explanation for how each of these criteria are met:

1. Minimal risk: The DAWA interventions do not introduce new diagnostic or therapeutic procedures and do not alter clinical care beyond reinforcing existing Ministry of Health and WHO guidelines. No experimental treatments or biological samples are involved. The day 7 phone calls pose minimal risk and involve no sensitive or clinical procedures.

2. Important Social Value: Improving antibiotic stewardship is a national and global priority due to rising antimicrobial resistance. The DAWA project directly supports Zanzibar's action plan on AMR by strengthening primary-care decision-making and reducing inappropriate antibiotic use, with expected long-term public health benefits.

3. Impracticability of Obtaining Written Consent: While written consent may be technically feasible, requiring signatures would still disrupt routine care, reduce participation (especially among low-literacy groups), and introduce systematic differences between participants and non-participants. Structured oral informed consent for day 7 follow-up phone calls, respects autonomy while maintaining feasibility and scientific integrity.

The waiver for informed consent of day 0 is also in line with the National Guidelines on Ethics for Health Research in Tanzania, as the study is using existing data (data from ZanEMR). The request for verbal consent of day 7 data is also in line with the Tanzanian guidelines as well as the CIOMS guidelines. Precedent for such a waiver exists for similar cluster randomized trials in Tanzania, Cambodia, and Vietnam.[94-96]

18.5.2 DAWA III – Before-After analysis

The DAWA III – Before-After analysis will not collect day 7 clinical outcome data, and will thus only rely on the routine data collected within ZanEMR and ZanEMR-AS. Thus, in line with the same principles outlined for the DAWA I and II – Cluster RCT, we request a waiver for individual written consent from individual participants.

18.5.3 Qualitative studies

Individual written consent will be requested from healthcare providers participating in qualitative semi-structured in-depth interviews and focus group discussions. The informed consent forms are found in Appendix A09 to A14.

18.6 Adverse events

As the study involves minimal risk to participants (quality improvement in adherence to national standard treatment guidelines), and this study is a close to real-world pragmatic study, all adverse events will be managed as per routine procedures by the health care providers providing care to the patients.

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19 DISSEMINATION POLICY

Results from the study will be disseminated through presentations at local, national, and international conferences, and will be published in leading medical journals as open access publications, targeting relevant clinicians, policy makers, and health intervention implementers. De-identified research data will be made available for reuse. The de-identified data will be accessible upon request for research purposes only through a secure data repository. Yearly meetings with a national advisory panel including clinicians, public health experts, patient representatives, and government officials will be conducted to share study results, in order for these panel members to further disseminate the findings to relevant stakeholders. Finally, study results will be communicated to participating health facilities and District Health Management Teams, with material shared to further disseminate findings to patients.

The study will be registered within clinicaltrials.gov and results will be reported accordingly on the platform.

Authorship for relevant conference abstract submissions and manuscript publications will follow the criteria for authorship recommended by the International Committee of Medical Journal Editors (ICMJE). Inclusion of coauthors from diverse background, including career-stage, gender, race, and ethnicity will be encouraged. To the best of the study team's abilities, any re-use of data by external research teams will be requested to include at minimum one co-author from the country of research (Tanzania). A lay summary of findings in Swahili will accompany major publications, and will be shared with communities, patients, and local health workers.

20 APPENDICES

20.1 Case Report Forms

A01_form 01 Baseline eCRF

A02_form 02 D7 follow-up eCRF

A03_Form 03 ZanEMR data

20.2 Qualitative data collection tools

A04_IDI HCW questionnaires

A05_ IDI HCW questionnaires Swahili translation

A06_IDI stakeholders questionnaires

A07_IDI stakeholders questionnaires_Swahili Translation

A08_Non Particiant Observation guide

20.3 Informed consent materials

A09_ICF IDI_HCP

A10_ICF IDI_HCP Swahili translation

A11_ICF IDI_stakeholders

A12_ICF IDI_stakeholders Swahili translation

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A13_ICF_Observation _HCP

A14_ICF_Observation _HCP Swahili translation

A15_oral consent script

A16_oral consent script Swahili translation

20.4 Study information leaflet

A17_study information flyer

A18_study information flyer Swahili translation

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