DYNAMIC Tanzania – MedAL-mentor ancillary study

Statistical Analysis Plan (SAP)

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Revision history

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1. Abbreviations and glossary of terms

CDSA	Clinical Decision Support Algorithm
CI	Confidence interval
CONSORT	CONsolidated Standards Of Reporting Trials
eCDSA	electronic Clinical Decision Support Algorithm
ePOCT+	Name of eCDSA (not an abbreviation)
GoT-HoMIS	Government of Tanzania -Hospital Management Information System
HCW	Health Care Worker
HF	Health Facility
IQR	Interquartile range
medAL-mentor	Name of a monitoring and benchmarking tool (not an abbreviation)
mRDT	malaria Rapid Diagnostic Test
MTUHA	Mfuma wa Taarifa za Uendeshaji Huduma za Afya (TZ health management information system)
STATA	Statistical software package (not an abbreviation)
TZ	Tanzania

2. Introduction

2.1. Background and rationale

ePOCT+ is a pediatric electronic clinical decision support algorithm designed for healthcare workers in primary care centers in Tanzania. The objective is to improve the integrated management of acutely ill children aged 1 day to 14 years and reduce inappropriate antibiotic prescription.

Preliminary findings from the first phase of the DYNAMIC project, a cluster randomized controlled study, indicate a significant decrease in antibiotic prescription from 70% of all consultations in the control arm to 23% in HFs using ePOCT+, with similar clinical outcomes at day 7. This is consistent with what has been reported in previous studies with earlier generations of this eCDSA.[1,2] However, in DYNAMIC, there was considerable variation in antibiotic prescription and uptake of ePOCT+ across different HFs. In addition, other studies using different eCDSA based on Integrated Management of Childhood Illness guidelines did not show any impact on antibiotic prescription.[3] Therefore, it is crucial to better understand the factors promoting the uptake of eCDSAs and influencing antibiotic prescription.

During the first phase of the DYNAMIC project in intervention HFs, mentoring of HCWs was conducted with a real-time monitoring and benchmarking dashboard known as medAL-mentor, which relied on data collected through ePOCT+. The tool consists of an interactive dashboard enabling the study team to review trends in antibiotic prescription and other clinical indicators for each HF. The team provided direct feedback to HCWs on their performance, and compared it with data from other HFs. The team found that mentoring facilitated by this near real-time audit, feedback, and benchmarking dashboard had benefits and potentially contributed to the observed results.

This is consistent with several articles in the literature highlighting the positive impact of auditing and feedback to improve antibiotic stewardship in primary care,[4-7] although in other studies this positive effect was rather modest or absent.[8,9] Benchmarking in healthcare - defined as “a process of comparative evaluation and identification of the underlying causes leading to high levels of performance”[10]- has also proven successful in primary care, not only in reducing antibiotic prescription but also in enhancing quality of care.[11-15] Indeed, benchmarking has been promoted for years by infectious disease societies as a component of hospital antimicrobial stewardship programs,[16] even if not always successful.[17] Of note, most of the feedback and benchmarking activities described in the literature have not been conducted in real-time but rather retrospectively, for instance on a monthly or quarterly basis. In addition, they required the intervention of an external party, whereas medAL-mentor also enables HCWs to access their results directly themselves. Finally, published initiatives have largely come from middle and high-income countries.[11] Overall, there is a lack of data and consensus regarding the impact of digital tools enabling real-time audit, benchmarking, and feedback on antibiotic prescription and quality of care.

The goal of this ancillary study is to reduce antibiotic prescription and improve quality of care for children in primary care in Tanzania using a near real-time monitoring and benchmarking dashboard (medAL-mentor), as well as feedback from the study team.

2.2. Research hypothesis

The null hypothesis is that there is no difference in antibiotic prescription between HFs with access to medAL-mentor and those without. The alternative hypothesis is that there is a difference between the two groups.

$H_0 : p_0 = p_1$

$H_1 : p_0 > p_1$

p_0 : antibiotic prescription in the control group

p_1 : antibiotic prescription in the intervention group

2.3. Study objectives

The primary objective of the study is to determine whether the provision of medAL-mentor, an online monitoring and benchmarking tool, decreases antibiotic prescription by primary care clinicians using a clinical decision support algorithm (ePOCT+) for the management of sick children.

Secondary objectives are :

a. To assess the impact of medAL-mentor on clinicians' uptake of ePOCT+

b. To assess the impact of medal-mentor on clinicians':
    a. Performance of key measurements and assessment of signs by clinicians
    b. Compliance with the recommendations related to point-of-care tests (for malaria and hemoglobin)

3. Study methods

3.1. Study design

MedAL-mentor study is an open-label, parallel cluster randomised controlled study embedded in the second phase of the DYNAMIC study in Tanzania. The intervention consists of providing direct access to medAL-mentor to the study team and to the HCWs. The study team will target calls and monitoring visits to HFs based on medAL-mentor indicators and use the dashboard to facilitate mentoring with HCWs. Since the intervention takes place at the HCW level and their practices are influenced by the context of the HF they are working in, randomization at the HF level rather than at the HCW level was chosen.
40 HFs using ePOCT+ for the first time during the second phase of the DYNAMIC project will be randomized into two groups (randomization 1:1, intervention: control).

In HFs allocated to the medAL-mentor arm, the intervention will consist of:

- Providing tablets with ePOCT+ and initial training for use by HCWs
- Initial training on antibiotic stewardship
- Access to medAL-mentor for HCWs and the study team
- Regular (at least every 2 weeks) supportive messages sent by the study team to HCWs providing feedback from medAL-mentor
- Targeted mentoring activities (via phone calls or HFs visits) provided by the study team, guided by the review of medAL-mentor

In HFs allocated to the control arm, tablets with ePOCT+ will also be provided to HCWs with initial training, but subsequent monitoring will be conducted routinely:

- Providing tablets with ePOCT+ and initial training for use by HCWs
- Initial training on antibiotic stewardship
- No access to medAL-mentor for HCWs or the study team
- At least one message sent by the study team to HCWs every two weeks, to inquire about any issues and trigger a call or site visit if needed
- At least one visit from the study team in each HF every two months.

The primary outcome measure is the antibiotic prescription rate as routinely documented by HCWs in the HFs (such as the MTUHA book or individual patient records). Secondary outcome measures are level of uptake of ePOCT+, antibiotic prescription rate as reported in medAL-reader, and other quality of care indicators (see below).

3.2. Sample size

The sample size was calculated to demonstrate an absolute reduction of 15% in antibiotic prescription in the intervention group, in a superiority analysis.
The intraclass correlation coefficient (ICC=0.08), the baseline antibiotic prescription (40%, in absence of medAL-mentor supervision), the cluster size (a conservative estimate of 80 patients/month/cluster, for 6 months), and the coefficient of variation for cluster sizes (0.6) were estimated from results of the first phase of the study. The duration (6 months) was chosen to consider the time required to induce change in HCWs' behavior and to evaluate their fatigue over time.
To have 80% power to detect an absolute difference of 15% of antibiotic prescription between the two arms, for a two-sided test at alpha of 0.05, we would require 13 clusters and 6240 participants per arm. Given the uncertainty in the estimation of the parameters used for the sample size calculation, the time estimated to induce change and in order to we decided to include all the available HFs, i.e. 20 clusters per arm.

3.3. Randomization

All 40 HFs part of the DYNAMIC project and using ePOCT+ for the first time during the second phase of the project (i.e. 20 HFs that were in the control group during the first phase of DYNAMIC, and 20 HFs newly included for the second phase) will be included in the medAL-mentor study. HFs will be randomized (1:1, intervention:control) to have access to medAL-mentor (intervention) or routine monitoring (control). Randomization will be stratified by number of patients/week (< or > 25 children under five per week) and by access to GoT-HoMIS (the Tanzanian Health Management Information System), to ensure balance of these variables in the two arms. Where possible, the exposure will be randomized 1:1 within strata and misfits will be reallocated to strata to get as good as possible overall balance (i.e. similarity between the two arms).[18]
An independent statistician will perform the randomization.

3.4. Timing of final analysis

Final analysis will be performed after collection of the outcome for 6 months in all 40 HFs included in the study (30 November 2023). All outcomes will be analysed collectively.

3.5. Timing of outcome assessments

The primary and secondary outcomes will be assessed with data recorded by the HCW at the time of the consultation (day 0).

4. Statistical principles

All applicable statistical tests will be 2-sided and will be performed using a 5% significance level. All confidence intervals presented will be 95% and two-sided.

4.1. Adherence and protocol deviations

Adherence to the medAL-mentor study protocol is assessed based on the percentage of :

Intervention HFs with :

- Access to medAL-mentor for HCWs and the study team
- Regular supportive messages (at least every 2 weeks) to HCW with feedbacks from medAL-mentor

- Targeted phone calls and visits based on medAL-mentor

Control HFs with :
- No access to medAL-mentor for HCWs and the study team
- At least one message every 3 weeks, to inquire about any issues and trigger a site visit if needed
- At least 1 visit every 10 weeks and at least 3 visits during the study period

% adherence $_{intervention}$ = (number HFs fulfilling intervention criteria above / total number of intervention HF)*100.
% adherence $_{control}$ = (number HFs fulfilling control criteria above / total number of control HF)*100%.

Descriptive statistics on the adherence will be provided by study arm (intervention and control).

The following are pre-defined major protocol violations at HF level with a direct bearing on the primary outcome :

Intervention HF:

Not having access to medAL-mentor for the HCWs or the study team during the entire study period

Control HF **:**

Having access to medAL-mentor for the HCWs and/or the study team any time during the study period

4.2. Analysis population definitions

Intention-to-treat analysis: This analysis includes all consultations in HFs included in the study, regardless of whether the HCWs used ePOCT+ and had access to medAL-mentor.

Per-protocol population: This analysis includes only consultations in HFs included in the study and that did not experience major protocol violation during the study period.

5. Trial population

5.1. Screening data

Screening data will be presented for all children visiting participating HFs (see eligibility criteria below).
The total number of days recruiting, the total number of consultations with screened children and the total number of consultations with enrolled participants will be presented. The number of excluded participants from the primary and secondary outcomes analysis (with the number of those who did not provide consent and those without data available) will be presented. The summary will be provided overall and by HF.

5.2. Eligibility

5.2.1. Health facility eligibility

HFs eligible for the medAL-mentor study are those included in the DYNAMIC study, and using ePOCT+ for the first time during the second phase of the DYNAMIC study :
- 20 HFs that were in the control group during the first phase of DYNAMIC
- 20HFs newly included for the second phase of the DYNAMIC study, selected purposively among HFs eligible for the first phase

(see SAP phase 1 for details on HF selection)

5.2.2. HCWs eligibility

All clinicians working in sampled HFs will participate to the medAL-mentor study.

5.2.3. Participants eligibility

A child is eligible for the medAL-mentor study if:

- they visit a HF included in the medAL-mentor study

AND

- they meet the following inclusion criteria and none of the following exclusion criteria:

Inclusion Criteria:

- Aged 1 day (24 hours) to 14 years (inclusive)
- Presenting for an acute medical or surgical condition

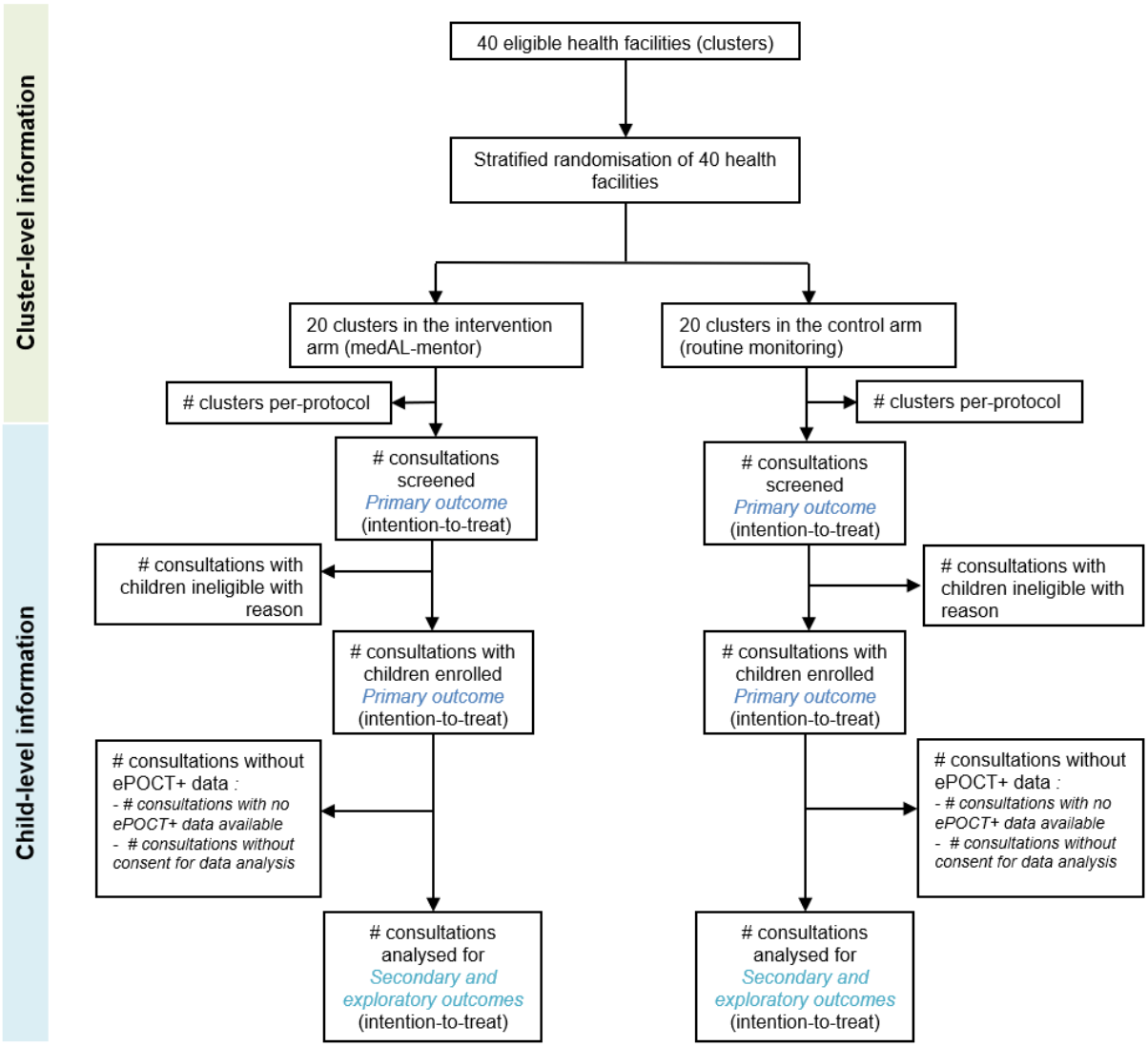
Exclusion Criteria:

- Presenting for scheduled consultation for a chronic disease (e.g. HIV, TB, NCD, malnutrition)
- Presenting for routine preventive care (e.g. growth monitoring, vitamin supplementation, deworming, vaccination).

Eligibility criteria will be assessed using the routine registry. For the primary outcome measure, all eligible participants will be included in the analysis.
For secondary and exploratory outcomes, whose measurement is based on ePOCT+ data, only participants managed with the tool will be included in the analysis. In addition, participants whose caregiver was unavailable, unable or unwilling to provide oral consent will be excluded from the analysis.

5.3. Recruitement

A CONSORT flow diagram will be used to summarise the number of consultations with participants who were screened and enrolled and the number of consultations analysed for secondary and exploratory outcomes.



5.4. Baseline HF and patient characteristics

The following baseline cluster (HF) characteristics will be summarized by study arm:
• HF type (dispensary or health center) and region
• Access to GoT-HoMIS
• Average number of patients under 15 seen per month by HF
• Baseline % antibiotic prescription by HF (as reported in ePOCT+) in the month before the start of the study (May 2023)

The baseline patient characteristics that will be summarized by study arm, and for the overall study include:
• Demographics: sex (number and percentage); age (median and IQR), age groups 0-2 months, 2 months - 5 years, 5-14 years (number and percentage) (for all included participants)
• Medical history: Main reasons for consultation - fever, respiratory, gastrointestinal, ear/nose/throat/mouth or skin complaint (number and percentage) (for participants with ePOCT+ data)
• Basic measurements: weight for age (median and IQR) (for participants with ePOCT+ data)

No formal statistical comparisons of baseline data will be performed.

6. Analysis

6.1. Outcome definition

6.1.1. Primary outcome

Percentage of children prescribed an antibiotic in the intervention group (medAL-mentor) as compared to the control group (routine monitoring)

Outcome measure: Number of children for whom at least one systemic (oral or parenteral) antibiotic has been prescribed during consultation, over all eligible children, as reported by the HCWs in the routine registry

Timing and method of assessment: documented by the HCW at the end of the consultation, in the routine registry (day 0)

Analysis type: superiority

6.1.2. Secondary outcomes

All secondary outcomes are compared between the intervention (medAL-mentor) and control (routine care) arms (superiority analysis).

a. Uptake of ePOCT+

Percentage of consultations with eligible children performed with ePOCT+

Outcome measure: number of consultations completed with ePOCT+, over all consultations with eligible children as reported in MTUHA books

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) and at the end of the consultation (routine registry), at day 0

Analysis type: superiority

b. Quality of care indicators

- **Percentage of children in whom key signs have been checked by HCWs**

Number of children in whom each of the key signs (temperature, weight, MUAC, respiratory rate) has been checked by HCWs, over the total number of children for whom this was recommended, as reported by HCWs in ePOCT+

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) at day 0

Analysis type: superiority

- **Percentage of children for whom appropriate diagnostic tests have been performed by HCWs**

Number of children for whom each of the diagnostic tests (haemoglobin and malaria tests) has been performed by HCWs, over the total number of children for whom the diagnostic test was recommended, as reported by HCWs in ePOCT+

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) at day 0

Analysis type: superiority

6.1.3. Exploratory outcomes

All exploratory outcomes are compared between the intervention (medAL-mentor) and control (routine care) arms.

a. Antibiotic prescription over time (longitudinal analysis)

Outcome measure: number of children for whom at least one systemic (oral or parenteral) antibiotic has been prescribed during consultation, over all eligible children, every week of the study period, as reported by the HCWs in the routine registry

Timing and method of assessment: documented by the HCW at the end of the consultation (routine registry) at day 0

b. Antibiotic prescription in children managed with and without ePOCT+

Outcome measure: number of children for whom at least one systemic (oral or parenteral) antibiotic has been prescribed during consultation, over all eligible children, as reported by the HCWs in the routine registry for children managed with and without ePOCT+

Timing and method of assessment: documented by the HCW at the end of the consultation (routine registry) at day 0

c. Antibiotic prescription reported in ePOCT+ versus in routine data (data consistency)

Outcome measure: number of children for whom at least one systemic (oral or parenteral) antibiotic has been prescribed during consultation systemic as reported by the HCW in ePOCT+ over number of children for whom at least one systemic (oral or parenteral) antibiotic has been prescribed during consultation systemic as reported by the HCW in the routine registry

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) and at the end of the consultation (routine registry) at day 0

d. Completion of ePOCT+

Outcome measure: number of consultations completed with ePOCT+, over all consultations started with ePOCT+

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) at day 0

e. Appropriate case management for malaria

Outcomes measure:
- % of consultations with febrile children tested for malaria
- % of consultations with children with a positive malaria test prescribed an antimalarial
- % of consultations with children with a negative malaria test prescribed an antimalarial
- % of consultations with untested children prescribed an antimalarial

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) at day 0

f. Appropriate case management for acute respiratory infections

Outcomes measure:
- % of children with acute respiratory infection prescribed an antibiotic
- % of children with bacterial pneumonia prescribed an antibiotic
- % of children with viral pneumonia prescribed an antibiotic
- % of children with cough/common cold prescribed an antibiotic

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) at day 0

g. Appropriate case management for diarrhea

Outcomes measure:
- % of children with acute diarrhea prescribed zinc
- % of children with acute diarrhea prescribed an antibiotic

Timing and method of assessment: documented by the HCW during the consultation (medAL-reader) on day 0

6.2. Analysis methods

Analyses will follow CONSORT guidelines.[19]
All the analyses will be carried out using generalized linear mixed models (GLMM, more specifically the multilevel logistic regression model with fixed and random-effects) to account for the complex multi-level structure of the data (induced by the stratified cluster randomized procedure), with individuals measurements nested within HCWs, who are themselves nested within HFs, which in turn are nested within districts, and at the highest-level districts are nested

within regions.[20] For the primary outcome, available risk factors at the individual level will be age category, sex, and type of final diagnosis (gastro-intestinal, respiratory, skin, malaria, other). For secondary outcomes, available risk factors at the individual level will be age, sex, child presenting with fever, gastro-intestinal, respiratory, ear/nose/throat/mouth and/or skin problem. In addition, to account for the correlation between the two exposure groups induced by the stratification, all the analyses will be adjusted for the stratification factors used in the randomization and not already accounted for (i.e. attendance rate and use of GoT-HoMIS) in the multi-level structure. Finally, the analyses will be adjusted by the baseline antibiotic prescription at each HF.

A special random-effects structure will be used at the HF level to account for unmeasured heterogeneity of the intervention effect[21] and confounding by cluster will be dealt with by separating within- and between-cluster effects using a partitioning method. [22,23]

Interactions (i.e. effect modification) between covariables (at the individual level) and exposure (i.e. medAL-mentor vs control) will be introduced into the model as fixed-effects. Variable selection will be based on clinical relevance and not on statistical tests of significance; consequently, no correction for multiple testing will be applied.[24]

To assess the impact of the intervention at the population level (i.e. the population averaged effect), the two marginal probabilities in the exposed and unexposed children will be computed by marginalization of the estimated conditional probabilities.[25,26] Based on these marginal probabilities, the marginal relative risk and marginal risk difference will be computed. These marginal parameters quantify the average impact of the intervention in the whole population, and to assess the impact of the intervention in specific subgroups of children marginal probabilities will be also computed in the subpopulations defined by the risk factors detailed above.

6.3. Missing data

Missing values will not be imputed given the great complexity of multiple imputations in the context of complex multi-level structures.[27]

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