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Delivery strategies for malaria chemoprevention in the post-discharge management of children hospitalised with severe anaemia or severe malaria: protocol for a cluster randomised controlled implementation trial in Benin

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ABSTRACT

Introduction Children discharged after in-hospital treatment for severe anaemia or severe malaria in sub-Saharan Africa remain at high risk of readmission and death, particularly in malaria-endemic settings where recurrent infections are common. Post-discharge malaria chemoprevention (PDMC) has demonstrated substantial reductions in mortality and hospital readmissions and is now recommended by the WHO. However, optimal PDMC delivery strategies, via existing health systems, that optimise adherence remain unclear, particularly in West Africa where implementation and evidence of impact on clinical outcomes are limited. This trial aims to determine the effectiveness of different PDMC delivery strategies and adherence support mechanisms in optimising completion of PDMC courses. Secondary objectives include assessing clinical outcomes (readmissions, outpatient visits, mortality), evaluating health system linkage mechanisms and examining the acceptability and feasibility of the different delivery approaches.

Methods and analysis A cluster-randomised implementation trial will be conducted in central and southern Benin across urban and rural settings. Clusters, defined as villages within the catchment areas of two referral hospitals, will be randomly allocated (1:1:1) to one of three arms: (A) facility-based drug distribution (all courses) at discharge with community health worker (CHW) home visit reminders; (B) monthly community-based drug delivery by CHWs combined with phone reminders; and (C) dispensing all courses to caregivers at discharge without adherence support (control). Eligible participants are children under 10 years hospitalised with severe anaemia or severe malaria and clinically stable at discharge. All participants should receive three courses of dihydroartemisinin–piperaquine at weeks 2, 6 and 10 post-discharge and will be followed for 14 weeks. The primary endpoint is incomplete adherence to the full PDMC regimen (3 courses/9 doses). Secondary endpoints include all-cause and malaria-specific readmissions, outpatient visits and mortality. Quantitative outcomes will be analysed using mixed-effects regression models under an intention-to-treat approach. Qualitative methods will assess acceptability and feasibility among caregivers, providers and policymakers.

Ethics and dissemination Ethical approval was received from the institutional review boards of the Benin

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Cluster-randomised trial design comparing two pragmatic post-discharge malaria chemoprevention (PDMC) delivery strategies, allowing direct evaluation of two distinct adherence-support approaches against standard facility-based dispensing to provide actionable evidence on the optimal PDMC delivery strategy for policymakers.
⇒ Integration of quantitative effectiveness outcomes with qualitative assessments of acceptability and feasibility.
⇒ Broad inclusion criteria and comprehensive follow-up, including children under 10 years old and multiple clinical outcomes (readmissions, clinic visits, mortality), providing both clinical and behavioural insights relevant for policy implementation.
⇒ Open-label trial implementation design may introduce performance and detection bias, while adherence assessment based on blister-pack collection and interviews remains vulnerable to social-desirability bias.
⇒ Cluster-randomised trial design comparing two pragmatic PDMC delivery strategies, allowing direct evaluation of two distinct adherence-support approaches against standard facility-based dispensing to provide actionable evidence on the optimal PDMC delivery strategy for policymakers.

Institute of Applied Biomedical Sciences and Liverpool School of Tropical Medicine. Trial findings will be disseminated to national and international stakeholders through meetings, peer-reviewed publications and major conferences to inform PDMC policy, implementation guidelines and global malaria scale-up efforts, particularly through engagement with the World Health Organization and major malaria funding partners

Trial registration number ClinicalTrials.gov, NCT06601712, registered on 14 September 2024 (https://clinicaltrials.gov/study/NCT06601712); and Pan African Clinical Trials Registry, PACTR202411682724094, registered on 5 November 2024 (https://pactr.samrc.ac.za/TrialDisplay.aspx?TrialID=31962).

INTRODUCTION

Severe anaemia is a major cause of morbidity and mortality among children in sub-Saharan Africa, particularly in areas with intense malaria transmission. It accounts for a substantial proportion of paediatric hospital admissions and in-hospital deaths.[1] Children who survive hospitalisation for severe anaemia or severe malaria remain highly vulnerable during the post-discharge period. Evidence shows that these children face an elevated risk of recurrent illness, hospital readmission and death in 6 months following discharge due to a combination of clinical, epidemiological, behavioural and nutritional factors.[2 3] In malaria-endemic settings, recurrent malaria infections represent one of the leading contributors to this excess post-discharge morbidity and mortality.[4 5]

A growing body of evidence highlights the magnitude of this problem. A study conducted in East Africa found that approximately one-third of children discharged from the hospital after recovery from severe anaemia were either readmitted or died within 6 months following discharge.[6] In areas with high malaria transmission, malaria was identified as one of the principal drivers of these adverse outcomes.[4 5] These findings underscore the importance of interventions that extend protection beyond the hospital stay and address the particularly vulnerable post-discharge period.

In response to this evidence, in 2022 the WHO included post-discharge malaria chemoprevention (PDMC) in its malaria guidelines.[7 8] The recommendation is based on a meta-analysis of three placebo-controlled, double-blind, randomised trials conducted in highly malaria-endemic settings among 3663 children hospitalised with severe anaemia.[9] Across these trials, administering PDMC for 3 months after hospital discharge resulted in substantial reductions in mortality and hospital readmissions. Specifically, PDMC was associated with a 77% reduction in mortality during the intervention period and a 55% reduction in all-cause hospital readmissions.[9] The protective effect was largely driven by reductions in severe malaria and severe malarial anaemia episodes after discharge. The benefits were greatest among children admitted with severe malarial anaemia but were also observed among children hospitalised for severe anaemia due to other causes.[6]

Several antimalarial regimens have been evaluated for PDMC. These include monthly sulfadoxine-pyrimethamine administered until the end of the malaria transmission season in The Gambia,[10] monthly artemether-lumefantrine in Malawi[5] and monthly dihydroartemisinin-piperaquine administered at weeks 2, 6 and 10 after hospital discharge in Uganda and Kenya.[6] All regimens demonstrated significant effectiveness in reducing post-discharge malaria episodes. In addition to its clinical impact, PDMC has been shown to be highly cost-effective and potentially cost-saving.[11] The main drivers of cost-effectiveness identified were avoided hospital readmissions and associated cost savings. Modelling studies estimate that large-scale implementation of PDMC across malaria-endemic regions of sub-Saharan Africa could prevent approximately 38 600 malaria-related hospital readmissions and 2176 deaths each year[12]; however, these figures are based only on children under five with severe anaemia and therefore likely underestimate the potential impact across the full target population. Consequently, several national malaria control programmes in East and Southern Africa have introduced PDMC in 2024 and 2025, including Kenya.[13]

Despite the strong evidence supporting PDMC, important operational challenges remain. Unlike other malaria prevention strategies, such as seasonal malaria chemoprevention (SMC), intermittent preventive treatment in pregnancy (IPTp), perennial malaria chemoprevention in infants (PMC, formerly IPTi) and the recently recommended malaria vaccines, PDMC does not yet have an established delivery platform within most health systems. This creates challenges for ensuring that children receive the full course of preventive treatment and that caregivers adhere to the recommended dosing schedule after discharge. Other key evidence gaps identified by WHO include coordination between hospital and community services, adherence at scale, costs and coverage of delivery strategies, integration with other malaria chemoprevention interventions (SMC and PMC) and combining PDMC with complementary interventions such as insecticide-treated nets (ITNs).

To date, only one implementation trial has evaluated different PDMC delivery approaches. This cluster-randomised trial conducted in Malawi compared two delivery strategies: one where caregivers were required to return to a health facility to receive each PDMC course, compared with one in which caregivers received all PDMC doses at the time of hospital discharge, along with instructions and scheduled administration dates recorded in the child's health booklet. Using a factorial design, community health workers (CHWs) and SMS reminders were also tested as adherence support strategies.[14] The study found that providing all PDMC doses to caregivers at discharge resulted in higher adherence than monthly collection at the facility. However, the trial was unable to draw firm conclusions about the effectiveness of the adherence support strategies because they were inconsistently implemented and only about 10% of caregivers received the planned SMS messages.[14] In addition, caregivers in the facility-based group were required to travel to tertiary

health facilities, which involved an average travel time of one to 3 hours, representing a substantial access barrier, impacting adherence.

Further research is therefore needed to identify optimal PDMC delivery strategies that maximise access and adherence in real-world settings. This includes evaluating alternative distribution platforms such as primary health facilities, as well as the potential role of mobile phone reminders and CHWs in supporting caregivers. Evidence from implementation research is essential to guide national policy decisions and ensure effective integration of PDMC into routine health services.

In countries such as Benin, where malaria remains a leading cause of severe paediatric illness, important data gaps persist regarding post-discharge outcomes. Recent hospital-based research conducted in southern Benin showed that approximately half of paediatric admissions are related to severe malaria and severe anaemia, often with fatal consequences.[15–17] However, data on hospital readmissions and mortality after discharge remain scarce. Generating context-appropriate evidence on post-discharge outcomes and evaluating feasible and cost-effective strategies for PDMC implementation are, therefore, essential to inform national malaria control policies and maximise the potential public health impact of this promising intervention in Benin.

STUDY OBJECTIVES

The primary objective is to determine the effectiveness of two different delivery mechanisms and adherence support strategies to optimise end-user adherence to PDMC. Secondary objectives are (i) to determine the clinical effectiveness of the different PDMC delivery strategies (all-cause and malaria-specific readmissions and sick-child clinic visits, all-cause mortality); (ii) to evaluate the effectiveness of the linkage mechanisms between the various health facility levels along the PDMC delivery continuum; and (iii) to determine the acceptability and feasibility of the different PDMC delivery and adherence support strategies. Additional health economics objectives include evaluation of the incremental cost per disability-adjusted life year (DALY) averted associated with alternative PDMC implementation support strategies, and are detailed in a separate protocol.[18]

METHODS AND ANALYSIS

Study area

The trial will be conducted in two malaria-endemic areas of Benin. Two public referral health hospitals have been selected based on several criteria, including the intensity of malaria transmission, the absence of competing malaria prevention strategies, the volume of hospital admissions, the capacity to manage severe anaemia and representation of both urban and rural contexts. The Mother and Child University Teaching Hospital Lagoon is located in Cotonou in southern Benin and operates in an urban setting, serving the populations of four major districts: Cotonou, Abomey-Calavi, Ouidah and Sèmè-Podji. In 2023, the facility recorded 2690 cases of severe malaria among 4388 hospitalised children. The Goho Departmental Hospital, located in a rural area approximately 136 km from Cotonou, provides services to the population of nine administrative districts (arrondissements). In 2023, the hospital reported 922 cases of severe malaria among 2764 hospitalised children. If recruitment rates are insufficient, the Mougnon Zone Hospital has been identified as a potential additional site. The malaria transmission pattern is similar across the three study sites, with two peak transmission seasons occurring from April to July and October to December. In southern Benin, insecticide-treated net (ITN) ownership generally exceeds 80%; however, utilisation among children under 5 years of age remains substantially lower, with only 50.4% sleeping under an ITN.[17] Nationally, the annual malaria incidence is 12.3%, compared with 6.6%, 6.5% and 10.2% in the Zou, Littoral and Atlantique departments, respectively.[19] In Benin, health facilities are connected to one or more villages, each served by CHWs employed by the Ministry of Health (MoH). CHWs make weekly household visits to provide basic healthcare and gather health data.

Trial design

The trial is a cluster randomised implementation trial with three arms at health facilities and their catchment communities (clusters) to evaluate two different delivery and adherence strategies (combined), which aim to enhance end-user adherence to the three PDMC courses, compared with a control arm of PDMC delivery without adherence support. The unit of randomisation will be health facility catchment villages to limit contamination related to adherence support within the community. The trial outcomes include clinical effectiveness, acceptability and feasibility, cost effectiveness and budget impact analysis. The health economics protocol will be published in a separate manuscript. Briefly, the economic evaluation will be conducted from a societal perspective and compare the cost effectiveness of the alternative delivery strategies over the 14-week follow-up period. Decision-analytic modelling using decision trees will estimate incremental costs, DALYs averted, hospital readmissions prevented, deaths averted and the cost per child completing the full PDMC course. Budget impact analyses and probabilistic sensitivity analyses will be conducted to assess affordability, uncertainty and the potential scalability of PDMC strategies within the routine health system in Benin.

Eligibility criteria

Clusters will be eligible if they correspond to villages or communities within the catchment areas of selected hospitals and are located in moderate-to-high malaria transmission settings.

Children eligible for pre-study screening will be those under 10 years of age hospitalised with severe anaemia

or severe malaria. Severe anaemia is defined as haemoglobin <5.0 g/dL, packed cell volume (PCV) <15% or the need for blood transfusion, while severe malaria requires parenteral artesunate and confirmed *Plasmodium* infection. Children with blood loss due to trauma, malignancy, known bleeding disorders or sickle cell disease, or body weight <5 kg will be excluded. Enrolment requires meeting screening criteria, clinical stability at discharge, haemoglobin ≥5.0 g/dL or PCV ≥15%, ability to take oral medication and feed, residence in the study area and caregiver consent. Additional exclusion criteria include prior enrolment, drug hypersensitivity, participation in another trial, planned surgery, non-resident in the study area and known heart conditions. HIV infection and cotrimoxazole prophylaxis are not exclusion criteria.

Interventions and randomisation

The intervention components, including choice of the drug regimen, delivery strategies and adherence support mechanisms, were finalised in-country by the study team and national-level stakeholders.[13] Following the formative research phase, the approach was refined during the annual meeting in Benin and subsequently validated through consultation with the MoH and key national public health stakeholders. This process was informed by formative research conducted under a separate, standalone protocol and a multi-stakeholder co-design workshop. PDMC will consist of three 3-day treatment courses of DP administered at weeks 2, 6 and 10 following hospital discharge. Two community-based delivery strategies combined with adherence support mechanisms will be evaluated during the trial.

Clusters, defined as villages within the catchment areas of participating health hospitals, will be randomly allocated in a 1:1:1 ratio to intervention arms (A and B) and the control arm (C). Cluster randomisation at the village level will be chosen to minimise contamination related to community-based adherence support. The cluster randomisation of villages will be stratified by health hospital sites and will be done before the start of the trial using the covariate-constrained method based on the distance to the health facility, the population density and the number of households per CHW, to achieve balanced allocation across study arms. The randomisation sequence will be generated by the trial statistician using a computer-generated covariate-constrained randomisation procedure. Multiple allocation schemes meeting the pre-specified balance criteria will be generated, and one randomly selected for implementation. Allocation will remain concealed until cluster assignment is completed, ensuring that investigators and recruitment teams do not have access to the allocation sequence and cannot influence cluster allocation. In Benin, a CHW is defined as a member of a community who provides basic health and medical care within their community, and is capable of providing preventive, promotional and rehabilitation care to that community, typically without formal education equal to that of a nurse or physician.

In Arm A, caregivers will receive all PDMC drugs at discharge, and CHWs will conduct monthly home visits to remind caregivers to administer the medication according to the PDMC schedule. In Arm B, PDMC drugs will be delivered to caregivers at home by CHWs, with additional reminders provided via phone calls by qualified community health workers (ASCQs). Arm C represents the control group (no adherence reminder), in which caregivers receive all PDMC drugs at discharge without additional adherence support (figure 1).

All participating children will receive standard in-hospital care for severe anaemia or severe malaria, including blood transfusion when indicated and parenteral artesunate, followed by a 3-day course of artemether–lumefantrine once the child is able to take oral medication, irrespective of the initial diagnosis. As part of routine clinical management, children may also receive parenteral antibiotics.

Outcomes

Effectiveness outcomes: The primary outcome is the proportion of children with incomplete adherence to the full courses of nine PDMC doses (three courses of three daily doses). Incomplete adherence will be defined as failure to administer all nine prescribed doses within 14 weeks after discharge. Secondary outcomes include: (i) the incidence of all-cause and malaria-specific readmissions within 14 weeks after discharge; (ii) the incidence of all-cause and malaria-specific sick-child clinic visits within 14 weeks after discharge; (iii) the incidence of all-cause mortality within 14 weeks after discharge (table 1).

Acceptability and feasibility outcomes: These include: (i) acceptability of the regimen among health providers, managers and policy stakeholders, as well as caregiver perceptions of PDMC, and adherence barriers and facilitators; (ii) perceptions among health providers, managers and policy stakeholders regarding the feasibility of each delivery strategy when implemented at scale, including required adaptations to routine practices to ensure effective implementation; and (iii) acceptability of the regimen and alternative delivery strategies among caregivers and CHWs across each trial arm (table 1).

Sample size

A sample size of 180 participants in the control arm (c) and 180 in each of the two intervention arms (A and B), for a total of 540 participants, will provide 90% power to detect a 50% reduction in the primary endpoint—the proportion of children with incomplete adherence to the nine PDMC doses—from 36.8% in the control arm to 18.4% (RR=0.50) in either intervention arm. The calculation assumes a 1:1:1 allocation ratio and accounts for multiple comparisons (α=0.025) as well as clustering due to participants from the same cluster (village) being followed by the same CHW. A small intra-cluster correlation coefficient (ICC) of 0.005 was assumed, which is more conservative than the ICC reported in Malawi (7.56×10^{-6}). It was deliberately chosen as a conservative

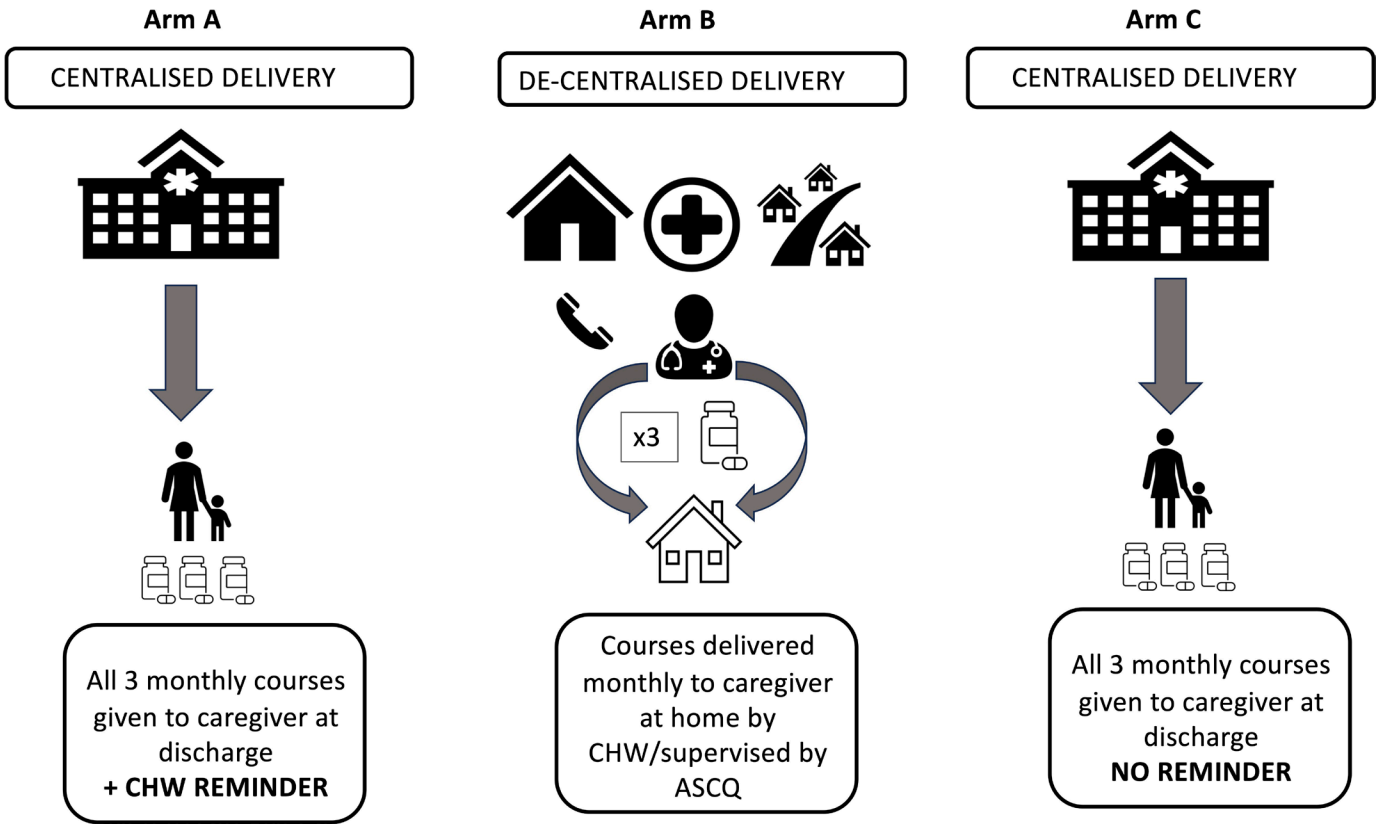

Figure 1 Study design (summary of trial arms). ASCQ, qualified community health workers; CHW, community health worker.

design assumption to account for the absence of reliable ICC estimates from comparable implementation studies in Benin and to accommodate potential between-cluster variability. To assess the robustness of the sample size assumptions, sensitivity analyses were performed across a range of plausible ICC values (online supplemental file 1). To allow for an anticipated 15% loss to follow-up, a total of 648 participants (216 per arm) will be recruited from the two health facilities.

Assignment of interventions: allocation and blinding

Restricted randomisation will be used to randomly assign the 710 clusters (villages) into the three study arms in a 1:1:1 ratio. The arms will be balanced based on the following factors: cluster population size, distance to the health hospital and number of households per CHW. Data on these variables will be collected by cluster through a baseline hospital-based cross-sectional survey conducted at the two study locations, as well as from the most recent general population census, and missing data will be imputed. Allocation at the cluster level will occur at the enrolled facilities before the start of the study. To promote community engagement, cluster allocation will be performed by community representatives selecting a sealed paper slip from an opaque bag, each indicating the assigned study arm.

Follow-up procedures

Caregivers of eligible children will be approached by dedicated study staff for potential participation during hospitalisation, and a consent form will be administered near or on the day of discharge. Two nurses will be assigned to each site to oversee recruitment. Under the study coordinator's supervision, they will schedule follow-up visits after randomisation. After consent is obtained and before discharge, household addresses will be collected, including caregivers' phone contacts. The study staff will conduct a household visit to accurately identify the home's location for future visits, including GPS coordinates to facilitate future identification of households.

Participants who have received standard in-hospital care for severe anaemia or severe malaria and any other condition will be recruited for PDMC before they are discharged from the hospital. PDMC will consist of three courses of DP at the end of weeks 2, 6 and 10 post-discharge. AL is the first-line treatment policy in Benin and is given at discharge in both sites. AL provides 2 weeks of post-treatment prophylaxis. Thus, the PDMC post-discharge courses with DP should commence at the end of the second week post-discharge. Participants will be followed through week 14 (ie, 4 weeks after the last PDMC course). Study staff will assess adherence by making unannounced home visits one to 3 days after the last dose of each course of medication. Using a structured questionnaire, they will collect blister packs and assess whether the study medication was administered to the child participating in the trial. The same visits will be used to assess safety endpoints, clinical effectiveness endpoints,

Table 1 Study outcomes and measurements by objectives

Objectives	Outcomes	Measurement
Primary		
To determine the effectiveness of different delivery mechanisms and adherence support strategies to optimise end-user adherence to PDMC	► Proportion of participants with incomplete adherence to the 9 doses of PDMC	Adherence assessed through caregiver-held treatment cards, remaining pill counts, and structured caregiver interviews at each follow-up visit (weeks 2, 6, and 10). Incomplete adherence defined as a number of PDMC intake tablets<9 doses. Proportion calculated as number of children with incomplete adherence divided by total enrolled participants per arm.
Secondary		
To determine the clinical effectiveness of the different PDMC delivery strategies (all-cause and malaria-specific readmissions and sick-child clinic visits, all-cause mortality)	► Incidence of all-cause and malaria-specific readmissions within 14 weeks after discharge ► Incidence of all-cause and malaria-specific sick-child clinic visits within 14 weeks after discharge ► Incidence of all-cause mortality within 14 weeks after discharge	Data collected through review of health facility registers, hospital records and caregiver reports during scheduled follow-up visits. Malaria-specific outcomes confirmed by diagnostic test (RDT or microscopy). Incidence rates calculated per child over the 14-week follow-up period. Mortality verified through caregiver report and/or community verification.
To evaluate the effectiveness of the linkage mechanisms between the various health facility levels along the PDMC delivery continuum	► Arm A: Proportion of CHWs who conducted a home visit to remind the caregiver about the child's first PDMC course within 2 weeks after discharge ► Arm B: Proportion of CHW who delivered the first PDMC course to the child at home within 2 weeks after discharge	CHW activity logs and supervision records used to document home visits and drug delivery. Verification through caregiver report during follow-up. Proportion calculated as number of eligible children receiving the intervention (home visit or drug delivery) within 2 weeks post-discharge divided by total eligible children per arm.
To determine the acceptability and feasibility of the different PDMC delivery and adherence support strategies	► Health provider, manager and policy stakeholder acceptability of the regimen and perceptions of caregiver acceptability and adherence ► Health provider, manager and policy stakeholder perceptions of the feasibility of each delivery strategy when implemented at scale, and adaptations to their working practices required to ensure effective implementation ► Caregiver and community health worker acceptability of the regimen and the alternative delivery strategies in each trial	Qualitative data collected through in-depth interviews (IDIs) and focus group discussions (FGDs) with caregivers, CHWs, health providers and stakeholders. Topic guides structured around acceptability and feasibility frameworks (eg, perceived burden, appropriateness, satisfaction). Data analysed thematically using NVivo 15 (QSR International). Where applicable, acceptability scores derived from structured questionnaires using Likert scales and summarised descriptively.

CHW, community health worker; PDMC, Post-discharge malaria chemoprevention.

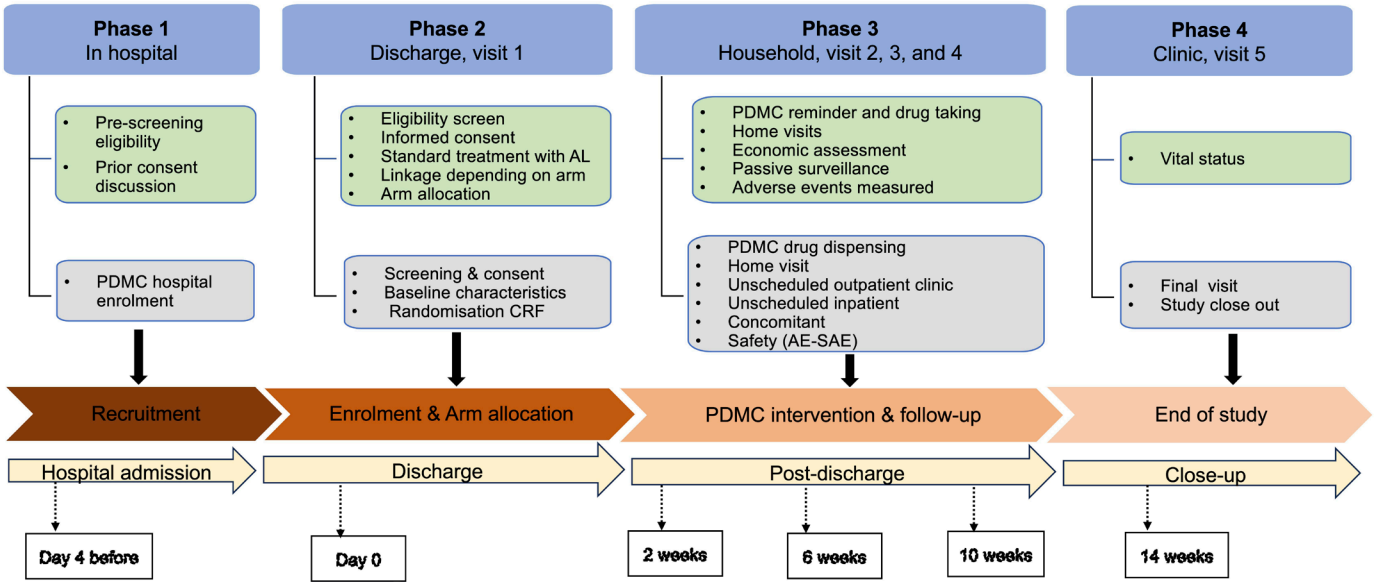

Figure 2 Study schedule. AL, artemether-lumefantrine; AE-SAE, adverse event/serious adverse event; CRF, case report form; PDMC, post-discharge malaria chemoprevention.

and beneficiary costs. Participants will be invited to the clinic at week 14 for an end-of-study visit. This will include a clinical assessment and participant cost assessment (for the health economics component) (figure 2).

The acceptability of alternative PDMC delivery channels and adherence support strategies will be assessed among providers, CHWs and caregivers' perspectives. In-depth interviews (online supplemental file 2) will be conducted with health facility managers, clinical staff and pharmacists (≈ 12–20 participants) to evaluate regimen acceptability, perceived caregiver adherence, feasibility at scale and required practice adaptations. National stakeholders, including decision-makers in malaria and child health programmes, will also be interviewed (≈ 5 participants). CHWs engaged in intervention arms will participate in interviews (≈20 participants) to explore their experiences, workload, costs and implementation challenges. Caregivers of enrolled children will be interviewed at home (≈ 15–24 participants) to assess acceptability, access and adherence barriers/facilitators. Six focus group discussions (≈ 8–12 participants per group) will complement findings. Participants will be purposively selected across study arms and adherence levels. The interviews and focus group discussions will be conducted by a senior social scientist and three researcher assistants from the Institut de Recherche Clinique du Benin (IRCB, Benin), with support from a social scientist and the trial principal investigator from the Liverpool School of Tropical Medicine (LSTM, UK).

Before the trial, several sensitisation activities will be conducted with providers, community health workers and local community leaders (heads of villages and sub-districts) to explain the purpose of the study. Meetings with on-site providers will also be held periodically to maintain their commitment to the trial procedures.

Data management

Quantitative data will be collected using standardised forms on RedCap and managed exclusively by authorised study staff. All case report forms will be securely stored in locked facilities until they are coded, verified and entered into a central database. Following data entry and cleaning, physical copies will be archived for a minimum of 2 years in secure facilities in line with local regulations, after which they will be destroyed. Electronic data will be retained in compliance with applicable data protection laws. Where relevant, study data may be linked to demographic and health surveillance systems using unique individual or household identifiers to enhance socio-demographic analyses. Data management procedures will include quality control measures to ensure data accuracy, completeness and traceability. REDCap validation rules, including range checks, mandatory fields and logical constraints, will minimise data entry errors. Audit trails will track database changes, users and timestamps, while version control procedures will ensure the use of approved study documents and databases. Final country-specific datasets will be archived at IRCB, while pooled RedCap datasets will be securely stored at the LSTM for at least 15 years.

Qualitative data will be managed under strict confidentiality procedures. Audio recordings and related data will be stored on password-protected systems with regular backups. Transcripts will be pseudonymised and identifying information stored separately. Interviews will be transcribed and translated into English or French, ensuring conceptual accuracy. Quality assurance will include checks of transcription and translation. Physical documents will be destroyed according to institutional policies and digital recordings deleted at study completion. Standardised identifiers will ensure traceability while preserving confidentiality. Pseudonymised datasets may be shared with other researchers, subject to ethical approvals, participant consent and institutional data governance policies.

Statistical methods

A detailed statistical analysis plan will be finalised prior to database lock and will supersede the study protocol. The trial profile will be presented as a Consolidated Standards of Reporting Trials (CONSORT)-compliant flow diagram, including the extension for cluster randomised trials, summarising the number of clusters and participants at each stage, from screening to analysis, as well as withdrawals, losses to follow-up and reasons for exclusions.

Baseline characteristics will be described for the overall population and by intervention group using appropriate summary statistics. The primary analysis will follow the intention-to-treat principle, including all randomised participants, analysed according to their assigned group. Secondary analyses will be conducted on the per-protocol population, excluding participants with major protocol deviations, while safety analyses will include all participants who received at least one dose of the intervention. Efforts will be made to minimise missing data, and reasons for omissions will be documented where possible. No imputation will be applied for missing primary outcomes in the main analysis. Sensitivity analyses will be conducted to assess the potential impact of missing data, including multiple imputation approaches if the missing rate is less than 20% and worst-case scenario assuming non-adherence. Missing baseline covariates will be imputed in adjusted analyses using appropriate multiple imputation methods with 10 imputations assuming missing at random.

The primary endpoint will be analysed using generalised linear mixed models with a log link and binomial distribution to estimate risk ratios (RR) and 95% CIs. The model will include intervention group as a fixed effect and will account for the cluster-randomised design by including a random intercept for village. Adjusted analyses will incorporate pre-specified covariates, including health hospital, rural/urban status, child age, baseline disease severity (severe malaria vs severe anaemia). In case of convergence issues, alternative approaches such

as removing random effects or using Poisson regression with robust standard errors will be applied.

Secondary endpoints will be analysed using similar modelling approaches, depending on outcome type. Binary outcomes will yield RRs, continuous outcomes will be analysed using Gaussian models to estimate mean differences. Count outcomes, including recurrent clinical events such as multiple hospital readmissions or sick-child visits, will be analysed using mixed-effects Poisson or negative binomial regression models, incorporating an offset for follow-up time when appropriate. Repeated events will be accounted for using participant-level random effects and cluster-level random effects to address within-child and within-village correlation.

Subgroup analyses will explore effect modification across key baseline characteristics, including age, disease severity and socioeconomic factors, and will be considered exploratory. Two primary intervention comparisons (intervention arm A vs control arm C and intervention arm B vs control arm C) will be performed. To control the overall type I error rate, multiplicity will be addressed using the Bonferroni correction for primary outcome (ie, 0.025 for each comparison) but not for secondary outcomes. Results will be presented with adjusted p-values and corresponding 95% CIs. All analyses will be performed using Stata V.17 (StataCorp, College Station, Texas, USA) or R V.4.5.1 (R Foundation for Statistical Computing).

Oversight and monitoring

A Data Safety and Monitoring Board (DSMB) will be established to provide oversight for the study. The DSMB members will be independent of the trial and its institutions and have the necessary expertise to monitor study progress and participant safety. The DSMB will be responsible for monitoring the progress of the trial, adherence to the protocol, the safety data and the critical efficacy endpoints.

The management of the trial is the responsibility of the chief investigator and country principal investigators. They will ensure that data are recorded in compliance with good clinical practice and that all regulatory and institutional requirements are adhered to.

All serious adverse events (SAEs) will be reported to the in-country principal investigator within 24 hours using a standardised electronic form capturing key details and causality assessment by the study clinician. Unexpected SAEs considered at least possibly related to the intervention will require expedited reporting within 48 hours of occurrence, with follow-up information submitted within 14 days if unresolved. Other adverse events will be summarised annually. Common, non-hospitalised childhood illnesses will not be routinely reported unless related to the intervention. All safety reporting will comply with regulatory and ethical requirements and be shared with relevant committees, authorities, the sponsor and stakeholders, including in the final study report.

Quality assurance will ensure compliance with Good Clinical Practice (GCP) and trial integrity. The sponsor oversees monitoring, with independent external visits at initiation, mid-study and close-out. Country principal investigators manage daily activities, staff delegation and training. Ongoing spot checks and corrective actions will ensure protocol adherence, data quality and regulatory compliance. A total of six monitoring visits, including the site initiation visit and the close-out visit, will be conducted by an independent clinical research organisation.

DISCUSSION

This protocol describes the first cluster-randomised implementation trial of PDMC delivery and adherence-support strategies in West Africa, addressing a critical evidence gap that has limited national-level uptake of the WHO recommendation. Children discharged after treatment for severe anaemia or severe malaria face a sustained period of high vulnerability, with recurrent malaria, secondary infections, nutritional deficiencies and suboptimal caregiving driving substantial readmission and mortality risk for up to 6 months and in some cases up to 18 months.[20 21] Severe acute malnutrition is also a leading underlying aetiology of severe anaemia.[15] PDMC, recommended by the WHO in 2022, has been shown to be both clinically effective and highly cost-effective, with potential to prevent tens of thousands of malaria-related hospital readmissions and thousands of deaths annually across sub-Saharan Africa.[9 11]

Despite strong evidence supporting its clinical efficacy, the implementation of PDMC faces significant operational challenges.[22 23] To date, very few countries have adopted this recommendation. Unlike other chemoprevention interventions, PDMC lacks a well-established delivery platform within most health systems. Barriers such as limited access to healthcare facilities, caregiver burden and inconsistent adherence to multi-dose regimens undermine its real-world effectiveness. Among the few feasibility studies conducted, delivering PDMC at discharge with all three courses given to the caregivers appears to enhance adherence to the prescribed number of doses.[14 24] However, the impact of additional adherence support strategies, such as SMS reminders or supervision by community health workers, remains unclear; in the Malawi implementation trial, only approximately 10% of caregivers received the planned SMS reminders, precluding firm conclusions about adherence support effectiveness. While PDMC is described as highly cost-effective, the main cost-drivers identified are likely to vary depending on implementation strategies.

This trial aims to address critical knowledge gaps by evaluating different strategies for delivering PDMC and providing adherence support in malaria-endemic regions of Benin. Using a cluster-randomised design, the trial will generate evidence on the relative effectiveness, feasibility and acceptability of two approaches: (i) caregiver receipt of all PDMC doses at hospital discharge with follow-up by CHWs and (ii) home-based delivery of PDMC by CHWs, supported by SMS reminders. This trial is the first PDMC

implementation trial in West Africa, where transmission patterns, drug-resistance landscapes and health-system structures differ from East Africa. It involves children aged under 10 years rather than children under five, as recommended by WHO, as well as children hospitalised with severe malaria without concomitant severe anaemia, in line with the September 2023 stakeholder consensus.[13] The trial also includes a comprehensive follow-up to assess clinical outcomes, including malaria-specific and all-cause readmissions, sick-child clinic visits and mortality. Additionally, the trial will evaluate adherence and acceptability, offering a robust assessment of both clinical and behavioural impacts.

Generating context-appropriate evidence in Benin is particularly crucial, as severe malaria and anaemia account for nearly half of paediatric hospitalisations in some regions.[15] There is a lack of randomised controlled trials evaluating the clinical effectiveness, as well as the delivery and adherence effectiveness of PDMC in West Africa. The findings from this trial, conducted in West Africa, a region with distinct malaria transmission patterns and socio-cultural contexts compared with East African settings, will inform policymakers and National Malaria Control Programmes.

This trial has several anticipated limitations. The implementation design is open-label by necessity, with potential for performance and detection bias mitigated by objective blister-pack adherence assessment and standardised case ascertainment. Adherence is verified via blister-pack collection and structured interview rather than pharmacological measurement, which carries some risk of social-desirability bias and pill dumping (unused pills prior to a home visit if they did not adhere to the full course). The 14-week primary follow-up captures the immediate intervention period; longer-term protective effects of PDMC will be addressed by the planned 6-, 9- and 12 month follow-up sub-study. Although villages were chosen as the unit of randomisation to minimise contamination, residual contamination between adjacent clusters cannot be entirely excluded. To minimise contamination, villages have been used as the unit of randomisation because CHWs operate within predefined village catchment areas and deliver intervention activities only to participants residing in their assigned villages. CHWs receive trial arm-specific training and are instructed not to implement intervention procedures outside their allocated clusters. Participant migration or receipt of intervention activities outside the assigned cluster will be documented throughout follow-up. Finally, the two participating sites, although chosen to capture both urban and rural contexts, may not fully represent the diversity of health-system settings in Benin or West Africa more broadly.

Finally, the findings will inform PDMC implementation guidance for the Benin Ministry of Health and the National Malaria Control Programme, with potential to extend to other West African settings sharing similar transmission and health-system contexts. Outputs will include practice-ready job aids and operational guidance co-developed with stakeholders to support scale-up beyond the trial sites, complementing global WHO recommendations and extending life-saving protection beyond hospital discharge.

ETHICS AND DISSEMINATION

Research ethics approval

The trial will follow the Declaration of Helsinki, GCP and national regulations in Benin. Protocols and consent materials have been approved by relevant ethics and regulatory committees, including Liverpool School of Tropical Medicine (N°24-020), the Institute of Applied Biomedical Sciences Ethics Committee (N°212 du 04/10/2024), the Beninese national drug regulatory agency ABMed (N°ABMED/2025D/2875/DHE/SA), the Benin national data protection agency (N°2025-244/APDP/Pt/AP/SC-R/SAOU/EB) and from MoH research department (Reference N°3175/MS/DC/SGM/DFRS/SRS/SA). Amendments require prior ethical approval and sponsor agreement before implementation and dissemination.

Informed consent procedures

Written informed consent will be obtained from caregivers in local languages before enrolment and maintained throughout participation (online supplemental files 3 and 4). The study will be clearly explained and consent confirmed once the child is stable and eligible. Illiterate participants will have an independent witness. All participants will be informed of their right to withdraw from the study at any time without affecting care. Copies of consent forms will be provided if desired.

For acceptability/feasibility components, trained research staff will obtain consent from all participants after providing study information. Stakeholders, health providers, community health workers and caregivers will be consented through appropriate procedures (written or recorded verbal), ensuring voluntary participation, confidentiality and no impact on employment or access to care.

Protection of privacy and confidentiality

All participant information will be treated as strictly confidential, with risks of disclosure minimised through secure storage and coded data systems. Personal identifiers will be replaced by unique study codes to protect identities while allowing necessary data linkage. Access to paper and electronic records will be restricted to authorised personnel only.

Data will be handled in accordance with legal and ethical standards, including the Benin and UK Data Protection Acts. Study outputs will present only aggregated data without identifying individuals. Data shared for analysis will be securely transferred and managed in compliance with international data protection requirements.

DISSEMINATION ACTIVITIES

On trial completion, findings will be shared with national stakeholders in Benin, including policymakers, government departments, academic institutions and professional bodies, through national meetings to inform decision-making and support the development of PDMC implementation tools and guidelines. Results will also reach the global malaria research community via peer-reviewed publications and presentations at major international conferences, including the American Society of Tropical Medicine and Hygiene and the WHO. Key international stakeholders and funders, such as Global Fund, the Foreign, Commonwealth & Development Office and the President's Malaria Initiative, will be informed to support broader malaria strategy scale-up. We will specifically target the WHO for developing global PDMC implementation guidance.

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